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(54) **Phanothiazone derivatives and analoga.**

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Description

BACKGROUND OF THE INVENTION

This invention involves certain phenothiazone derivatives and analogs. These compounds are usaful as inhibitors of mammalian leukotriene biosyntheais. As such, these compounds are useful therapeutic agents for traating allergic conditions, asthma, cardiovascular disorders and inflammation.

The leukotrienes are a novel group of biologically active mediators derived from arachidonic acid through the action of lipoxyganase enzyme systems. There are two groups of leukotrienes darived from the common unstable precursor Leukotriene A_4. The first of these are the paptido-lipid leukotrienes, the most important being Leukotrianes C_4 and D_4. These compounds collectively account for the biologically active material known as the slow reacting substance of anaphylaxis.

The leukotrienes are potent smooth muscle contracting agants, particulalry on respiratory smooth muscle but also on other tissues (e.g. gall bladder). In addition, they promote mucous production, modulate vascular parmeability changes and are potent inflammatory agents in human skin. The most important compound in the second group of leukotrienes is Leukotriene B_4, a dihydroxy fatty acid. This compound is a potent chemotactic agent for neutrophils and eosinophils and in addition, may modulata a number of other functions of these cells. It also effects other cell types such as lymphocytes and for example may modulate the action of T-suppressor cells and natural killer cells. When injected *in vivo*, in addition to promoting the accumulation of laukocytes, Leukotriene B_4 is also e potent hyperalgesic agent and can modulate vasculer permeability changes through a neutrophil dependent mechanism. Both groups of leukotrienes are formed following oxygenation of arachidonic ecid through the action of a 5-lipoxygenase enzyme. See for example, D. M. Bailey *et al., Ann. Rpts. Med. Chem. 17* 203 (1982).

Raspiratory Conditions

a) *Asthma.* The leukotrienes are potent apasmogens of human trachea, bronchus end lung parenchymal stripa, end when sdministered to normsl volunteers as aerosols are 3,800 times more potent than hlstamine et inducing a 50% decrease in air flow at 30% of vital capacity. They mediate incraasea in vascular permeability in animala and promote mucoua production in human bronchial explants. In addition, Leukotriane B_4 may also mediaté mucoua production and could be an important mediator of neutrophil and eosinophil accumulation in esthmatic lungs. 5-Lipoxygenase products are elso thought to ba regulators of msst cell degranulation end recent studiea with human lung mast cells have suggested that 5-Lipoxygenaae inhibitors, but not corticosteroids, may auppress antlgen-induced mast call degranulation. *in vitro* studies have shown that entlgen chellenge of buman lung reaults in tha release of laukotrienes snd in addition purified human mast cella can produce substantial amounts of leukotrienas. There is therafore good evidence that the leukotrienes are important mediators of human asthma. 5-Lipoxygeneae inhibitors would therefore be a new class of drugs for the traatmant of asthma. Sae for example, B. Semuelsson, *Science 220* 568—575 (1983).

Skin Diseaaea

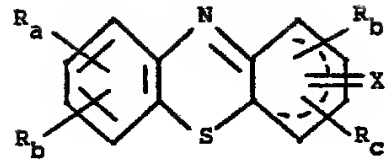
a) *Psoriasis.* Psoriasis la e human skin disease whlch effects between two and alx parcent of the populatlon. Thee is no adequate therapy for psoriaala and related skln conditlons. The avidance for leukotriane involvement In these diseases is as follows. One of the earliest events in tha development of prepapillery lesions ls the recruitment of leukocytes to tha skin site. Injectlon of Laukotriene B_4 into human skin resulta in a pronounced neutrophil sccumulation. There are gross sbnormalities in erachidonic scid metabolism in human psoriatic skin. In particular, highly elevated levels of frea arachidonic acid can be measured as well as large amounts of lipoxygenese products. Leukotriene B_4 has been detactad in psoriatic lesions, but not in uninvolved skin, in biologically slgnificant amounts.

Allergic Conditions

a) Leukotrienes can be measured in nasal washings from patients with allergic rhinitis and are greatly elevated following antigen challenge. Leukotrienes may mediate this disease through their ability to regulate mast cell degranulation, by modulating mucous production and mucocillary clearance and by mediating the accumulation of inflammatory leukocytes.

Leukotrienea can also madiate other diseases. These include atopic darmatitis, gouty arthritis and gall bladder spasms. In addition, they may have a role in cardiovascular disease because leukotrienes C_4 and D_4 act aa coronary and cerebral arterial vasoconstrictors and these compounds may also have negative inotropic effects on the myocardium. In addition, the leukotrienes are important mediators of inflammatory diseases through their ability to modulate leukocyte and lymphocyte function.

A number of Phenothiazone derivatives of the general Formula:

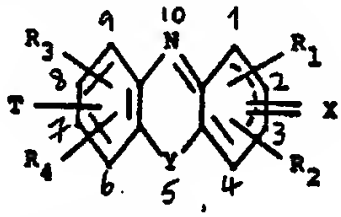


A

especially when X is O are taught in the literature; see for example Terdic *et al., Rev. Roum. Chim. 13,* 833—8 (1968; Beckett *et al., Xenobiotica 8,* 721—36 (1978); Panea *et al., Rev. Roum. Chim. 25,* 691—5 (1980); Bhargava *et al.,; Gazz. Chim. Ital. 110,* 201—3 (1980); Bodea *et al., Ann. Chem. 698,* 186—90, (1966); Sugita *et al., Nippon Kagaku Zasshi 89,* 309—15 (1968); Broser *et al., Rev. Roum. Chem. 17,* 1747—53 (1972); Bodea *et al., Ann. Chem. 715,* 122—7 (1968); Bodea *et al., Rev. Roum. Chim. 13,* 971—6 1241—4 (1968); Sugita *et al.,* Japanese Patent No. 73, 22,714 (1973); Tsyino, *Tet. Lett.* (10), 763—6 (1969); Roseboum *et al., J. Pharm. Sci. 66,* 1395—8 (1977); Shakii *et al.,* Yakugaku Zasshi *86,* 541—3 (1966); Bodea *et al., Ann. Chem. 614,* 171—6 (1958); Collier *et al., Can. J. Med. Sci. 31,* 195—201 (1953); and Collier *et al., Can. J. Med. Sci. 30,* 443—6 (1952). However, none of the compounds of Formula A is taught to have mammalian leukotriene biosynthesis inhibitor activity.

It has been discovered that compounds of Formula A and especially those where X is O are effective inhibitors of mammalian leukotriene biosynthesis and are thus useful therapeutic egents for treeting conditions such as esthme, ellergies, inflammation and certain skin diseeses in humans.

This invention provides the use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of *a* compound of the Formula I, e compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound:



I

in which

X is in the 1 or 3 position end is O, S or NR;

R is H, C_{1-6} branched or linaar alkyl, CN or phenyl;

Y is O, Se, S, SO, SO_2 or NR; and tha broken line represents a double bond between the 1 and 2 or 2 and 3 positions;

each of R_1, R_2, R_3 and R_4 independently of tha others, is

(1) hydrogan,

(2) C_{1-6} alkyl,

(3) C_{2-6} alkanyl,

(4) $-(CH_2)_n$ M

where n is 0 or en integer from 1 to 6 and M is

(e) OR_5,

(b) halogen,

(c) CF_3,

(d) SR_5 where R_5 is H; C_1—C_6 alkyl; benzyl; phenyl or substituted phenyl where the substituents are C_{1-3} elkyl, halogen, CN, CF_3, $COOR_6$, CH_2COOR_6, $(CH_2)_nNR_8R_9$ where n is 0, 1 or 2, C_{1-3} alkoxy, OH or C_{1-6} haloalkyl; $-(CH_2)_mCOOR_6$, where m is 0 or an integer from 1 to 6 and R_6 is H, phenyl or C_{1-6} alkyl; CN, formyl, CF_3 or CH_2-R_{12}, where R_{12} is C_{1-5} alkyl, phenyl or dimethylamino;

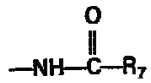
(e) phenyl or substituted phenyl as defined above for R_5;

(f) $COOR_6$;

(g) 

where R_{14} is H, $(CH_2)_n$ $COOR_8$ where n is 0 or an integer from 1 to 4, C_{1-6} elkyl, CF_3, phenyl, or substituted phenyl as defined above for R_5;

(h) tetrazole;

(i) 

where R_7 is C_{1-6} alkyl, benzyl or phenyl;

(j) —NR_8R_9 where R_8 and R_9 are independently selected from H, phenyl or substituted phenyl as defined above for R_5 or C_{1-4} alkyl, C_{1-4} alkylaminoalkyl, or may be joinad through tha N to form a 4-mathyl piperazinyl radical;

(k) —$NHSO_2R_{10}$ where R_{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl or CF_3;

(l) —C(=O)—CH_2OH;

(m) —SOR_{11} where R_{11} is C_{1-6} alkyl, phanyl or substituted phenyl as defined above for R_5, $(CH_2)_mCOOR_8$ whare m is 1 to 6, CN, formyl or CF_3;

(n) —$CONR_8R_9$;

(o) —$SO_2NR_8R_9$;

(p) —SO_2R_{13} where R_{13} is OH, H, C_{1-6} alkyl, phenyl or substituted phenyl as defined above for R_5, $(CH_2)_mCOOR_6$ where m is 1 to 6, CN or CF_3;

(q) NO_2;

(r) —O—C(=O)—R_{14};

(s) —O—C(=O)—NR_8R_8;

(t) —O—C(=O)—OR_7;

(u) —CN; or

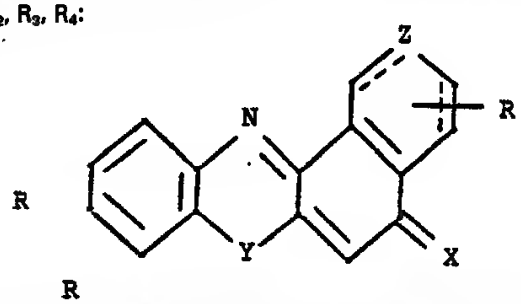
(v) $NR_{15}R_{16}$ whara R_{15} and R_{16} are such that $HNR_{15}R_{26}$ is an essential amino acid;

or any two of R_1,-R_2, R_3 and R_4 ara joined to form a fourth saturated or unsaturated C_{5-6} ring; and

T is H, halogan or CF_3.

Certain compounds of Formula (I) are novel and constituta anothar embodiment of tha invantion.

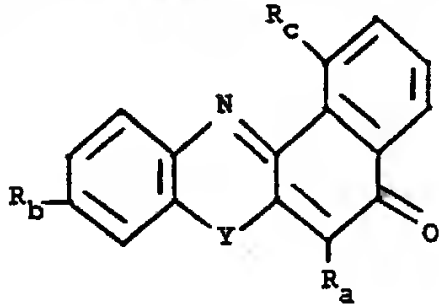
The numbars surrounding Formula I designate the substituent positions. T, R_1, R_2, R_3 and R_4 may be positioned anywhere in the structure. R_1, R_2, R_3 and R_4 may also be joined, a.g. as —$(CH_2)_{3-4}$—, to add a fourth ring to the basic three ring structure. This fourth ring may have five or six carbon atoms and may be saturated or unsaturated. For axampla, compounds of Formula II may be preparad by linking two of the substituents groups; R_1, R_2, R_3, R_4:



II

wherein Z may be CH, CH_2 or a bond, the broken lines represent optional doubla bonds and R represents tha substituent groups of Formula I (R_1, R_2, R_3, R_4 and/or T) not used to create the fourth ring.

The preferred compounds of Formula II have the structure II(a):



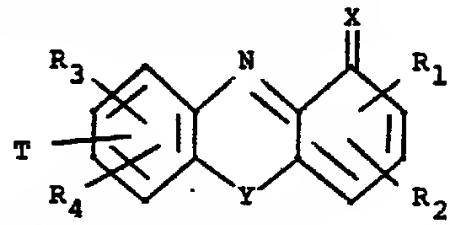
II(a)

wherein R_a is selected from hydrogen, halogen (F, Br, Cl, I), CH_3, CF_3, COR_d, NHR_d, SR_d and OR_d; R_b is selected from hydrogen, halogen (F, Br, Cl, I), CH_3, CF_3, CH_2OH, OR_d, SR_d, COR_d, $COOR_d$, CH_2COOR_d and $CH(CH_3)COOR_d$; R_d is hydrogen, phenyl, C_{1-4} straight or branched alkyl; R_c is selected from hydrogen or OR_d; and Y is selected from O, S, SO or SO_2.

Where possible, appropriate pharmaceutically acceptable salts of Formula I are included e.g., carboxylic or mineral acid addition salts where Formula I is basic and metal salts e.g. Na, K, NH_4 where Formula I is acidic.

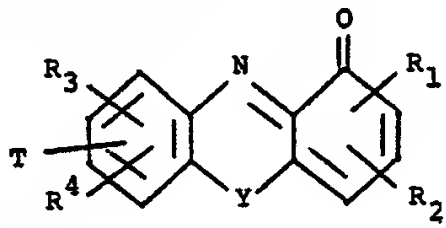
The term alkyl, unless indicated otherwise, indicates straight chain, branched chain and cycloalkyl groups. The term halogen or halo, unless otherwise indicated, includes Cl, Br, I and F.

A group of preferred compositions contain a compound of the Formula:



I(a)

More preferred Formula I(a) compounds are those wherein X is O or NH and Y is S, O, SO or SO_2. Still more preferred I(a) compounds are those having the Formula:



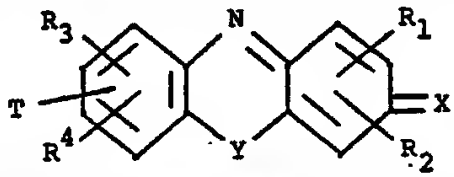
I(a)

wherein:

a) T, R_3 and R_2 are hydrogens,
b) T, R_1, R_2 are hydrogens,
c) T, R_3 and R_4 are hydrogens,
d) T, R_1, R_2, R_3 are hydrogens or
e) T, R_3, R_4, R_2 are hydrogens.

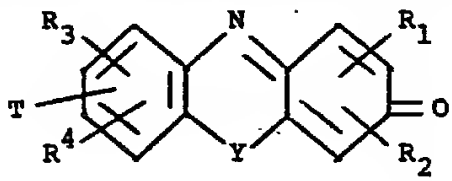
wherein R_1, R_2, R_3, R_4 and T are as defined for Formula I.

Another group of preferred compositions contain compounds of the Formula I(b):



I(b)

More preferred compounds of Formula Ib are those having the Formula wherein X is O or NH and Y is O, S, SO, SO_2. Still more preferred compounds of Formula I(b) are those of the formula I(c):



I(c)

I(c)

wherein:

a) T, R_3 and R_2 are hydrogens,
b) T, R_1, R_2 are hydrogens,
c) T, R_3 and R_4 are hydrogens,
d) T, R_1, R_2, R_3 are hydrogens,

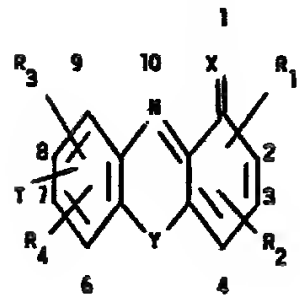
e) T, R_3, R_4, R_2 are hydrogens,
f) T, R_3 and R_4 are hydrogens and R_1 is in position 4,
g) T, R_3, R_2 ara hydrogens and R_1 is in position 4,
h) T, R_4, R_3, R_2 are hydrogens and R_1 is in position 4,
i) R_2 and R_3 are hydrogens,
j) R_1 and R_2 are hydrogens,
k) R_3 and R_4 are hydrogens,
l) R_2, R_3 are hydrogens and T is in position 4,
m) T and R_3 are hydrogens and R_2 is in position 4,
n) T and R_3 ara hydrogens and R_1 ia in position 4 and R_2 is in position 2,
o) T and R_3 are hydrogens and R_4 is in position 7, R_2 is in position 4 and R_1 is in position 2.
(p) T is hydrogen, R_1, R_2, R_3, and R_4 are in positions 1, 2, 4 and 7, respectively.

A particularly preferred series of Formula I(c) compounds are those in which n = 0 or 1 in the unit $(CH_2)_nM$.

Examples of Formula I compounds useful in the present compositions are tabulated below. In each of the tables the numbers preceding the T and the R_1—R_4 definitions indicate the substituent position in the structure.

TABLE 1

Compounds of the Formula



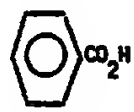
Number	Y	X	R_1	R_2	R_3	R_4	T
1	O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
2	O	O	2-t-Bu	H	4-Me	H	H
3	N—CH_3, S, O, Se, SO or SO_2	O	2-Cl	H	H	H	H
4	"	O	2-SCF_3	H	H	H	
6	"	O	2-S 	H	H	H	H
6	"	O	2-CN	H	H	H	H
7	"	O	H	3-CO_2Et	H	H	H
8	"	O	H	3-Cl	H	H	H
9	"	O	H	H	4-Cl	H	H
10	"	O	H	H	4-SO_2CH_3	H	H
11	"	O	2-Cl	H	4-Cl	H	H
12	"	NH	2-Cl	H	4-Cl	H	H
13	"	NH	H	H	H	H	H
14	N—CN	O	2-Cl	H	4-Cl	H	H
15	S	O	H	H	H	H	H
16	S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
17	S	O	2-Br	3-Br	4-Br	7-Br	9-Br
18	S	O	H	H	H	7-SO_2CH_3	H
19	S	O	2-Cl	H	4-SO_2CH_3	H	H
20	S	O	2-F	H	4-Cl	H	H
21	S	O	2-Br	H	H	H	H

TABLE 1 continued

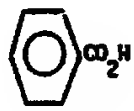
Number	Y	X	R_1	R_2	R_3	R_4	T
22	S	O	2-CF_3	H	H	H	H
23	S	O	2-SCF_3	H	H	H	H
24	S	O	2-SO_2CF_3	H	H	H	H
25	S	O	H	3-Cl	H	H	H
26	S	O	H	3-CO_2Et	H	H	H
27	S	O	H	3-CO_2H	H	H	H
28	S	O	H	3-CN	H	H	H
29	S	O	H	3-SCF_3	H	H	H
30	S	O	H	H	4-Cl	H	H
31	S	O	H	H	4-SCF_3	H	H
32	S	O	H	H	4-Cl	H	H
33	S	O	2-Br	H	4-Br	H	H
34	S	O	2-Cl	H	H	8-CN	H
35	S	O	2-Cl	H	H	8-CO_2Et	H
36	S	O	2-Cl	H	H	8-CO_2H	H
37	S	O	2-Cl	H	H	8-CF_3	H
38	S	O	2-Cl	H	H	7-SO_2CH_3	H
39	S	O	H	3-$CONMe_2$	H	H	H
40	S	O	2-Cl	H	H	7-OCH_3	H
41	S	O	2-S 	H	H	H	H
42	S	O	2-SO_2CH_3	H	H	H	H
43	S	O	2-$CH_2CH{=}CH_2$	H	4-$CH_2CH{=}CH_2$	H	H
44	S	O	H	3-$N(CH_3)_2$	H	H	H
45	S	O	H	H	4-Cl	7-S—C_6H_6	H
46	S	O	2-CH_2CO_2H	H	H	H	H
47	S	O	2-Cl	H	4-SCH_2CO_2H	H	H
48	S	O	2-$COCH_3$	H	H	7-OCH_3	H
49	S	O	H	H	4-CO—C_6H_5	7-OCH_3	H
50	S	NH	2-Cl	H	4-Cl	H	H

TABLE 1 continued

Number	Y	X	R_1	R_2	R_3	R_4	T
51	S	NH	H	3-$N(CH_3)_2$	H	H	H
52	S	NH	2-SCH_3	H	4-SCH_3	H	H
53	S	O	H	H	H	H	H
54	S	NH	H	H	H	H	H
55	S	NH.HCl	H	H	H	H	H
56	S	O	H	H	H	H	H
57	O	O	H	H	H	H	H
58	O	NH	H	H	H	H	H
59	O	S	H	H	H	H	H
80	O	NH.HCl	H	H	H	H	H
61	Se	O	H	H	H	H	H
62	Se	NH	H	H	H	H	H
63	Se	S	H	H	H	H	H
64	NH	NH.HCl	H	H	H	H	H
65	NH	S	H	H	H	H	H
66	O	O	4-Cl	H	H	H	H
67	O	O	4-Cl	H	7-OMe	H	H
68	O	O	4-Me	H	H	H	H
69	O	O	H	2-Cl	H	H	H
70	O	O	4-Cl	2-S-pPAA*	H	H	H
71	Se	O	4-Cl	H	H	H	H
72	Se	O	4-Cl	H	7-OMe	H	H
73	Se	O	4-Me	H	H	H	H
74	Se	O	4-Cl	2-S-pPAA*	H	H	H
75	N—CH_3	O	4-Cl	H	H	H	H
76	N—C_6H_6	O	4-Cl	H	7-OMe	H	H
77	N—H	O	4-Cl	2-S-pPAA*	H	H	H
78	S	O	4-Cl	H	H	H	H
79	SO	O	H	H	H	H	H
80	SO_2	O	H	H	H	H	H
81	SO_2	O	4-Cl	H	H	H	H

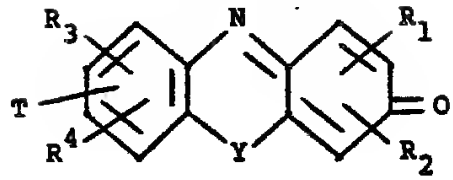
TABLE 1 continued

Number	Y	X	R_1	R_2	R_3	R_4	T
82	N—Me	O	H	H	H	H	H
83	N—Me	O	4-Cl	H	H	H	H
84	N—Me	O	4-Cl	H	7-OMe	H	H
85	N—Me	O	4-Br	H	7-OMe	2-OMe	H
86	NCN	O	4-Br	H	7-OMe	2-OMe	H
87	NCN	O	4-Cl	H	H	H	H
88	NH	O	2-Cl	H	H	H	H
89	NH	O	4-Cl	H	H	H	H
90	S	O	2-t-Bu	4-t-Bu	H	H	H
91	S	O	2-t-Bu	4-t-Bu	9-OMe	H	H
92	S	O	2-t-Bu	4-t-Bu	7-F	H	H
93	S	O	2-t-Bu	4-t-Bu	7-Me	H	H
94	S	O	2-t-Bu	4-t-Bu	7-SMe	H	H

*p-PAA = para-phenylacetic acid

TABLE 2

Compounds of the Formula



Number	Y	R_1	R_2	R_3	R_4	T
95	S	H	H	H	H	H
96	S	2-Cl	H	H	H	H
97	S	H	H	6-Cl	H	H
98	S	H	H	7-Cl	H	H
99	S	H	H	8-Cl	H	H
100	S	H	H	9-Cl	H	H
101	S	1-Cl	H	H	H	H
102	S	1-Cl	4-Cl	H	H	H
103	S	2-Cl	4-Cl	H	H	1-Cl
104	S	2-$N(Me)_2$	H	H	H	H
105	S	2-SMe	H	H	H	H
106	S	2-S-pPAA	H	H	H	H
107	S	2-$C(O)CH_3$	H	H	H	H
108	S	2-OMe	H	H	H	H
109	S	H	H	H	7-CH_2CO_2H	H
110	S	H	H	H	8-CH_2COOH	H
111	S	H	2-SO_3	H	H	H
112	S	2-$N(Me)_2$	H	H	H	H
113	S	2-SMe	H	H	H	H
114	S	2-$C(O)CH_3$	H	H	H	H
115	S	2-OMe	H	H	H	H
116	S	2-CH_2CO_2H	H	H	H	H
117	S	2-$CH(CH_3)CO_2H$	H	H	H	H
118	S	4-CH_2COOH	H	H	H	H
119	S	4-$CH(CH_3)CO_2H$	H	H	H	H
120	S	H	H	7-OH	6-propyl	H

TABLE 2 continued

Number	Y	R_1	R_2	R_3	R_4	T
121	S	4-Cl	H	H	H	H
122	S	4-F	H	H	H	H
123	S	4-F	H	7-Cl	H	H
124	S	4-Et	H	H	H	H
125	S	4-Et	H	7-OMe	H	H
126	S	4-Et	H	7-Cl	H	H
127	S	4-Cl	H	7-OMe	H	H
128	S	4-OMe	H	7-Cl	H	H
129	S	4-Cl	H	6-Cl	H	H
130	S	4-Cl	H	8-Cl	H	H
131	S	4-Cl	H	9-Cl	H	H
132	S	4-Cl	H	6-OMe	H	H
133	S	4-Cl	H	8-OMe	H	H
134	S	4-Cl	H	9-Et	H	h
135	S	4-Cl	H	6-Et	H	H
136	S	4-Cl	H	7-Et	H	H
137	S	4-Cl	H	8-Et	H	H
138	S	4-Cl	1-Et	H	H	H
139	S	4-Cl	2-Et	H	H	H
140	S	4-Cl	1-CH_2COOH	H	H	H
141	S	4-Cl	2-CH_2COOH	H	H	H
142	S	4-Cl	H	6-CH_2COOH	H	H
143	S	4-Cl	H	7-CH_2COOH	H	H
144	S	4-Cl	H	8-CH_2COOH	H	H
145	S	4-Cl	2-$N(Me)_2$	H	H	H
146	S	4-Cl	1-$N(Me)_2$	H	H	H
147	S	4-Cl	2-$N(Me)_2$	7-OMe	H	H
148	S	4-Cl	2-$N(Me)_2$	7-Cl	H	H
149	S	4-Cl	2-SMe	H	H	H
150	S	4-Cl	2-SCH_2COOH	H	H	H

TABLE 2 continued

Number	Y	R_1	R_2	R_3	R_4	T
151	S	4-Cl	2-S-pPAA	H	H	H
152	S	4-Cl	1-S-pPAA	H	H	H
153	S	4-Cl	2-S-pPAA	7-OMe	H	H
154	S	4-Cl	2-SO_3H	H	H	H
155	S	4-Cl	2-OMe	H	H	H
156	S	4-Cl	2-OMe	7-Cl	H	H
157	S	4-Cl	H	7F	H	H
158	S	4-OMe	H	7-OMe	H	H
159	S	4-OMe	H	7-Me	H	H
160	S	4-OMe	2-SMe	H	H	H
161	S	4-SMe	H	H	H	H
162	S	4-Br	H	H	H	H
163	S	4-I	H	H	H	H
164	S	4-Br	H	7-OMe	H	H
165	S	4-I	H	7-OMe	H	H
166	S	4-Br	2-Me	H	H	H
167	S	4-I	2-Me	H	H	H
168	S	4-Cl	H	7/8-$(CH_2)_4$—		H
169	S	4-Cl	H	7/8-$(CH_2)_3$—		H
170	S	4-Br	2-OMe	7-OMe	H	H
171	S	2-OMe	7-OMe	H	H	H
172	S	1-OMe	7-OMe	H	H	H
173	S	2-OMe	7-OMe	H	H	1-Br
174	S	1-OMe	7-OMe	H	h	2-Br
175	S	1-OMe	7-OMe	H	H	4-Br
176	S	1-OMe	7-OMe	H	H	2-Cl
177	S	1-OMe	7-OMe	H	H	4-Cl
178	S	2-OMe	7-OMe	H	H	1-Cl
179	S	2-OMe	7-OMe	H	H	4-Cl
180	S	2-OEt	7-OEt	H	H	1-Br

TABLE 2 continued

Number	Y	R_1	R_2	R_3	R_4	T
181	S	2-OEt	7-OEt	H	H	4-Br
182	S	2-OEt	7-OEt	H	H	1-Cl
183	S	2-OEt	7-OEt	H	H	4-Cl
184	S	2-OMe	7-OMe	8-OMe	H	1-Br
185	S	2-OMe	7-OMe	8-OMe	H	4-Br
186	S	2-OMe	7-OMe	H	H	4-F
187	S	2-OMe	7-OMe	H	H	4-CF_3
188	S	2-OMe	7-OEt	H	H	4-Br
189	S	2-OMe	7-OEt	H	H	4-Cl
190	S	2-OMe	7-OEt	H	H	4-F
191	S	2-OMe	7-OEt	H	H	4-CF_3
192	S	2-OEt	7-OMe	H	H	4-Br
193	S	2-OEt	7-OMe	H	H	4-Cl
194	S	2-OEt	7-OMe	H	H	4-F
195	S	2-OEt	7-OMe	H	H	4-CF_3
196	S	1-OMe	2-OMe	7-OMe	H	4-Br
197	S	1-OMe	2-OMe	H	H	H
198	S	1-OMe	2-OMe	H	H	4-Br
199	O		Same as Numbers 90—198			
200	SO_2	4-OH	H	H	H	H
201	SO_2	1-OMe	2-OMe	4-CH_3	H	H
202	SO_2	2-OMe	7-OMe	4-OH	H	H
203	SO_2	2-OMe	4-OH	H	H	H
204	SO_2	1-OMe	4-OH	H	H	H
205	SO_2	2-Me	4-OH	H	H	H
206	SO_2	2-Cl	4-OH	H	H	H
207	SO_2	2-OEt	7-OEt	4-OH	H	H
208	SO_2	2-SO_2Me	4-OH	H	H	H
209	SO_2	4-OMe	H	H	H	H
210	SO_2	2-OMe	4-OMe	7-OMe	H	H

TABLE 2 continued

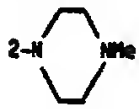
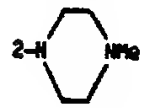
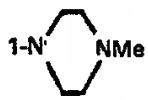
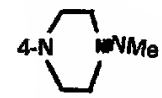
Number	Y	R_1	R_2	R_3	R_4	T
211	O	1-CO_2H	4-OH	7-NMe_2	H	H
212	O	1-Cl	2-Cl	4-Cl	H	7-Cl
213	S	9-OMe	H	H	H	H
214	S	2-OMe	H	H	H	H
215	S	2-OMe	4-OMe	H	H	H
216	S	1-OMe	2-OMe	4-Me	H	H
217	S	4-OMe	H	H	H	H
218	S	1-OMe	7-OMe	H	H	4-Br
219	S	1-OMe	7-OMe	2-Cl	H	4-Cl
220	S	1-OMe	7-OMe	H	H	4-Cl
221	S		7-OMe	H	H	H
222	S		7-OMe	H	H	4-Br
223	SO_2	2-OMe	4-OH	7-OMe	H	H
224	SO_2	1-NHPr	4-NHPr	H	H	H
225	SO_2			H	H	H
226	SO_2	2-OMe		7-OMe	H	H
227	SO_2	2-OMe	7-OMe	H	H	H
228	SO_2	2-OMe	4-NHPr	7-OMe	H	H
229	S	1-NHPr	4-NHPr	H	H	H
230	S	1-NHPr	4-NHPr	7-OMe	H	H
231	S	1-NHPr	4-NHPr	H	H	H
232	S	2-NHPr	4-NHPr	7-OMe	H	H
233	S	2-OMe	4-NH_2	7-OMe	H	H
234	S	2-OMe	4-NHPr	7-OMe	H	H

TABLE 2 continued

Number	Y	R_1	R_2	R_3	R_4	T
235	O	1-OMe	4-Cl	7-OMe	H	H
236	O	1-OMe	4-Br	7-OMe	H	H
237	O	1-NHPr	4-NHPr	H	H	H
238	SO_2	1-OMe	4-CN	7-OMe	H	H
239	SO_2	2-OMe	4-$NHCH_2CO_2R$*	7-OMe	H	H
240	SO_2	2-OMe	4-S-7-Bu	7-OMe	H	H
241	SO_2	2-OMe	4-CH_2CO_2R*	7-OMe	H	H
242	SO_2	2-OMe	4-SO_2Me	7-OMe	H	H
243	S	2-S-n-Bu	H	H	H	H
244	S	4-S-n-Bu	H	H	H	H
245	S	2-Me	4-S-n-Bu	H	H	H
246	S	2-OMe	7-Me	H	H	4-Br
247	S	2-OMe	7-CF_3	H	H	4-Br
248	S	2-OMe	7-F	H	H	4-Br
249	S	2-OMe	7-Cl	H	H	4-Br
250	S	2-OMe	7-Br	H	H	4-Br
251	S	2-OMe	7-NMe_2	H	H	4-Br
252	S	2-OMe	7-SMe	H	H	4-Br
253	S	2-OMe	7-SO_2Me	H	H	4-Br
254	S	2-OMe	7-Ph	H	H	4-Br
255	S	1-Me	H	H	H	H
256	S	2-Me	H	H	H	H
257	S	2-OEt	H	H	H	H
258	S	7-Cl	H	H	H	H
259	S	9-Cl	H	H	H	H
260	S	7-F	H	H	H	H
261	S	7-Me	H	H	H	H
262	S	7-OMe	H	H	H	H
263	S	2-Cl	H	H	H	H

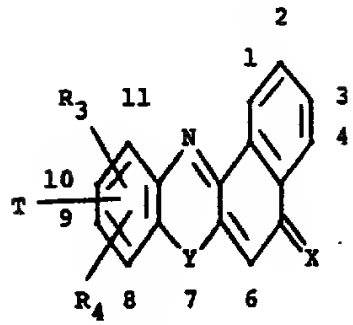
*R is H or C_1C_4 alkyl.

TABLE 2 continued

Number	Y	R_1	R_2	R_3	R_4	T
264	S	1-Me	7-Me	H	H	H
265	S	1-Me	7-Me	H	H	H
266	S	2-OMe	7-OEt	H	H	H
267	O	2-NH_2	H	H	H	H
268	O	7-OH	H	H	H	H
269	O	COMe	H	H	H	H
270	SO_2	2-OMe	7-OMe	H	H	4-Br
271	S	2-NHPr	4-NHPr	H	H	H
272	S	2-Cl	H	H	H	4-Cl
273	S	1-Me	7-Me	H	H	4-Cl

TABLE 3

Compounds of the Formula



Example	Y	X	R_3	R_4	T
1	O	O	H	H	H
2	S	O	H	H	H
3	SO	O	H	H	H
4	SO_2	O	H	H	H
5	SO	O	H	H	6-Cl
6	S	O	6-$COCH_3$	H	H
7	S	O	6-CH_3	H	H
8	SO_2	O	6-OH	H	H
9	SO_2	O	6-OMe	H	H
10	S	O	9-OMe	H	H
11	S	O	6-OH	H	H
12	S	O	6-OMe	H	H
13	S	O	6-NHCOMe	H	H
14	S	O	6-NHPh	H	H
15	S	O	H	H	6-Br
16	S	O	6-NHMe	H	H
17	S	O	6-NH-t-Bu	H	H
18	S	O	6-NH-COMe	H	9-Cl
19	S	O	6-NH-COMe	9-Ome	H
20	S	O	6-NHPh-p-Br	H	9-Cl
21	O	O	H	H	6-Cl
22	O	O	H	H	6-Br
23	O	O	9-OMe	H	6-Br

TABLE 3 continued

Example	Y	X	R_3	R_4	T
24	O	O	9-OMe	6-NHPr	H
25	S	O	6-CF_3	H	H
26	S	O	6-S-n-Bu	H	H
27	S	O	6-OMe	H	9-Cl
28	S	O	9-OMe	H	6-Cl
29	S	O	6-OMe	9-OMe	H
30	S	O	6-Cl	9-Me	11-Br
31	S	O	6-NHPh	9-Me	11-Br
32	S	O	6-Me	H	H
33	O	NH	9-NMe_2	10-Me	H
34	O	NH	9-$N(Et)_2$	H	H

A quite specific embodiment of the present invention is represented by the tripeptide γ-Glutamylcysteylglycine derivatives: 2-5-glutathionyl-3H-phenothiazin-3-one and 4-chloro-2-5-glutathionyl-phenothiazine-3-one.

The compounds of the Formula I have unexpected activity as inhibitors of the mammalian biosynthesis of leukotriene B_4, as well as leukotrienes C_4, D_4, E_4 and F_4, the active elements of the slow reacting substance of anaphylaxis (SRS—A). The compounds of Formula I act as inhibitors of the mammalian 5-Lipoxygenase enzyme system of the arachidonic acid cascade. This inhibition of the mammalian biosynthesis of leukotrienes indicated that the compositions would be useful to treat, prevent or ameliorate, in mammals and especially in humans 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjuntivitis and the like, 3) inflammation such as arthritides, 4) pain, 5) skin conditions such as psoriasis and the like and 5) cardiovascular conditions such as angina.

Representative compounds of Formula I have been tested using one or more of the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity and other relevant activities.

RBL—1 5-Lipoxygenase

Rat basophilic leukemia (RBL—1) cells were sonicated and centrifuged at 125000 xg. The resulting supernatant fraction was incubated with arachidonic acid (labelled with ^{14}C) to convert a portion of it to ^{14}C—5(S)-hydroxyicosatetraenoic acid (5—HETE). Compounds being evaluated as inhibitors of 5-Lipoxygenase were added prior to the addition of arachidonic acid. 5—HETE was isolated by extraction and paper chromatography, and quantitated by determining the amount of radioactivity (cpm) associated with 5-HETE.

Reference: Egan, R. W., Tischler, A. M. Baptista, E. H., Ham, E. A., Soderman, D. D., and Gale, P. H., *Advances in Prostaglandin, Thromboxane and Leukotriene Research 11* 151 (1983), (Samuelson, B., Ramwell, P. W., and Paoletti, R. (eds.), Raven Press, N.Y.

Mouse Macrophage Assay

Mouse peritoneal macrophages were treated sequentially with arachidonic acid (labelled with tritium); the compound being evaluated as an inhibitor, and a stimulator (zymosan). Metabolites derived from arachidonic acid (PGE_2, 6-keto $PG-F_{1\alpha}$ and leukotriene C_4) were separated from the incubation medium by extraction and chromatogrephy, and then quantitated by determining the amount of radioactivity (Cpm) associated with each of them. Inhibitors caused a reduction in the amount of radioactivity (cpm) associated with a given metabolite. (This protocol is identical to that described in the reference exept that the radioactivity herein associated with the LTC_4 was determined by counting an aliquot of the final aqueous solution directly rather than chromatographing it first).

Reference: Humes, J. L. *et al., J. Biol. Chem. 257,* 1591—4 (1982).

Antigen Challenge 'in vitro' Assay

Male guinea pigs weighing 300—350 g were sensitized by injecting (I.P.) ml of a suspension containing 0.4 mg of egg albumin (Ovalbumin, Grade V, Sigma Chemical Co.) and 4.0 g aluminum hydroxide in 19.6 ml of saline. Two weeks were permitted for sensitization to occur.

Three sensitized guinea pigs were stunned and exsanguinated. The tracheas were removed, freed of adhering tissue and divided longitudinally by cutting through the cartilaginous tissue directly opposite the muscle insertion. Each opened trachea was then transected between every second cartilage. Four of the cut sections were tied together, end to end, in a series with a No. 7 silk thread ensuring thet the tracheal muscles were all in the same vertical plane. Thue, each chain consisted of tissue from three different animals.

The chain so formed was then suspended under 1 g of tension (by silk ties at each end) in a 20 ml organ bath containing 10 ml of modified* Krebs-Henseleit buffer solution gassed with 95% O_2 and 5% CO_2 at 37°C. Mepyramine (0.55 µg/ml) and indomethacin (2.67 µg/ml) were added to the buffer to avoid the contribution of histamine receptors and cyclooxygenase products to the contrection. To record responses one end of the tracheal chain was attached to a Gould-Statham UC—2 force displacement transducer which wes connected to a Beckman Type R-dynograph. The preparations were allowed to equilibrate for one hour during which time the tissues were automatically washed (10 ml volume displacement) every 6 minutes.

Aftar the equilibration period the tissues were primed with mathacholine (3 µg/ml; 1.5×10^{-5}M), washed and eliowed to recover to baseline. The tissues were treated again with a second doae of methacholina, washed, eliowed to return to baseline and washed for an additional hour.

Two chains were usad as a controi. These ware incubated in a concentration of egg albumin sufficient to induce an avarage contraction of 50—80% of the mathacholina response.

Each compound to be teated was added to two other baths (at a final concentration in each bath of 10 µg/ml) 15 minutea prior to challenging the fresh cheins with egg albumin.

The response of the challengad tissue was expressed as a percentaga of tha methacholine maximum. Tha % inhibition for each compound waa then calculated. Compounds which at 10 µg/ml (final conc.) inhibited tha egg albumin response by 50% or more ware ratested at a iowar concentration.

Asthmatic Rat Assay

Rats were obtainad from an Inbrad lina of asthmatic rats. Both female and male rats from 200 to 300 g ware usad.

Egg albumin (EA), grade V_a crystallized and iyophilized, was obtained from Sigma Chemical Co., St Louis. *Bordatella pertussis* vaccine, containing 30×10^9 kiled bacteria per ml waa obtained from the Institut Armand-Frappier, Laval des Rapides, Quebec. Aluminum hydroxide waa obtainad from the Regis Chemical Company, Chicago.

Tha challenga and subaequent respiratory racordinga were carried out in a claar plaatic box with internal dimansions 10 × 6 × 4 inches. Tha top of tha box was removsble; in usa, it waa held firmly in placa by four clamps and an airtight seal waa maintained by a soft rubber gesket. Through tha centar of aach end of tha chamber a Davilbiss nabulizar (No. 40) was inaarted via an airtight seal and aach and of tha box also hed an outlat. A Fleisch No. 0000 pneumotachograph waa insertad into ona end of tha box and couplad to a Graas volumetric pressure transducer (PT5—A) which was then connected to a Backman Typa R Dynograph through appropriate coupiers. Whiia aerosolizing the antigen, tha outlets were opan and the pneumotachograph was isolated from the chamber. The outlets were closed and the pnaumotachograph end the chamber were connected during the recording or the respiratory patterns. For chailenge, 2 ml of a 3% solution of entigen in aaline was placed into each neubuiizer and the aerosol was generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

Rats were sensitized by injecting (s.c.) 1 ml of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saiina. Simultaneously, they received an injection (I.p.) of 0.5 ml of *B. pertussis* vaccine. They were used between days 14 and 18 postsensitization. in order to eliminate the serotonin component of the responae, rats were pretreated intravenously 5 minutes prior to aerosol challenge with 30 mg/kg methylserzide. Rats were then exposed to en aerosol of 3% EA in saline for exectly 1 minute, then their respiratory profiles were recorded for a further 25—30 minutes. The duration of continuous dyspnoea was meaaured from the respiratory recordings.

Compounda were generally administered either intraperitoneally 1 hour prior to challenge or orelly 1½ hours prior to challenge. They were either dissoived in dimethylsulfoxide or suspended in 0.1% methocel and 0.5% Tween 80. The volume injected has 2 ml/kg (intraperitoneelly) or 10 ml/kg (orally). Prior to oral treatment rats were starved overnight. Their activity was determined in terms of their ability to decrease the duration of symptoma of dyspnoea in comparison with a group of vehicle-treated controls. Usually, a compound was evaluated at a series of doses and an ED_{50} was determined. This was defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

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*modified Krebs solution in grams/liter and (mM):
NaCl — 6.87 (120); glucose — 2.1 (11); $NaHCO_3$ — 2.1 (25); KCl — 0.32 (4.72); $CaCl_2$ — 0.28 (2.5); $MgSO_4.7H_2O$ — 0.11 (0.5); KH_2PO_4 — 0.16 (1.2); pH at bathing solution = 7.35 ± 0.05.

PAF-Induced Hyperalgesia Assay

Female Sprague-Dawley rats, 35—40 g were fasted overnight. Platelet activating factor, PAF, (L-lecithin B-acetyl O-alkyl) 1 µg/0.1 ml was given by subplantar injection in the rat paw. The compounds to be evaluated were homogenized in Aqueous Vehicle (0.9% benzyl alcohol, 0.5% Tween 80 and 0.4% methylcellulose) and administered orally in a volume of 0.1 ml, 30 minutes prior to PAF.

Animals were tested 1, 2, 3 and 4 hours after PAF administration. The vocalization threshold, defined as the pressure (mmHg) needed to evoke a squeak response, was recorded for both the injected and contralateral paw. No animal was subjected to pressure greater than 60 mmHg. Hyperalgesia is defined as a decrease in vocalization threshold as compared to a normal paw. Percent inhibition of hyperalgesia was calculated as the proportion of animals with vocalization thresholds greater than 200% of controls.

Brewer's Yeast Hyperalgesia Assay

The standard method* for yeast hyperalgesia was used. Female Sprague-Dawley rats, 35—40 g were fasted overnight. A 5% solution (volume 0.1 ml) of Brewer's yeast was injected into the rat paw. The compound was homogenized in aqueous vehicle and given orally 2 hours after yeast. Vocalization thresholds were recorded 1 hours after drug (3 hours after yeast). Percent inhibition of hyperalgesia wes determined by the proportion of animals with vocalization thresholds greater than 25 mmHg.

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* Winter, C. A. *et al., J. Pharm. Exp. Ther. 150,* 165—171 (1965).

Following is data obtained using these various assays with representative compounds of Formula I.

TABLE 4

Assay Results

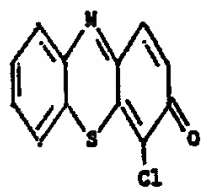
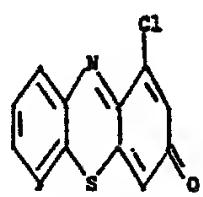
Test No.	Compound	Macrophage Ic50 (µg/ml)	RBL-1 Ic50 (µg/ml)	In Vitro Antigen Challenge Test µg/ml end % Inhibition
1		0.2	0.01	10 µg (100%) 1 µg (44%)
2		0.5	0.01	10 µg (68%)
3		0.2	—	10 µg (25%)
4		0.1	0.01	10 µg (100%) 1 µg (77%) 0.3 µg (42%)

TABLE 4 continued

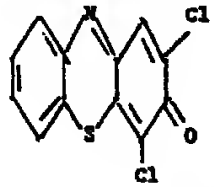
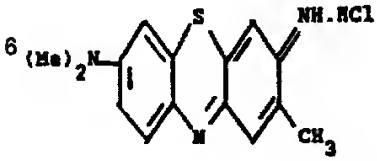
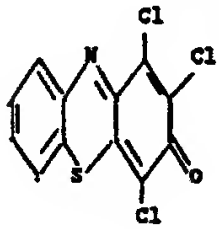
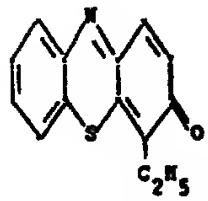
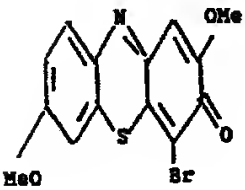
Test No.	Compound	Macrophage Ic50 (µg/ml)	RBL-1 Ic50 (µg/ml)	In Vitro Antigen Challenge Test µg/ml and % Inhibition
5		0.1—0.5	65% at 0.05 µ g/ml	10 µg (45%)
6		10% at 0,05 µg/ml		10 µg 24%
7		15% at 0.5 µg/ml	—	10 µg 37%
8		33% at 0.1 µg/ml	—	—
9		75% at 5 µg/ml	—	—
10		—	—	10 µg (100%)
11		0.1	—	3 µg (23%)

TABLE 4 continued

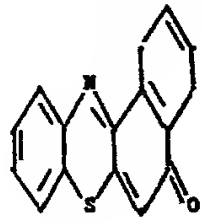
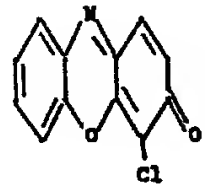
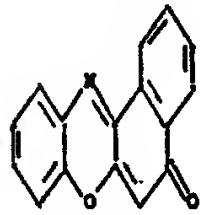
Test No.	Compound	Macrophage Ic50 (µg/ml)	RBL-1 Ic50 (µg/ml)	In Vitro Antigen Challenge Test µg/ml and % Inhibition
12		0.1	—	10 µg (55%)
13		—	—	3 µg (54%)
14		0.1	—	—

TABLE 5

Asthmatic Rat Assay Results

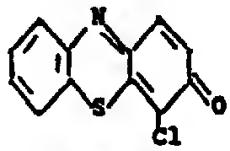
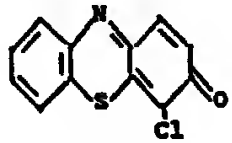
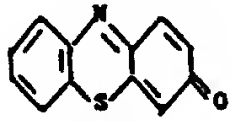
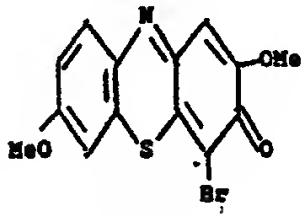
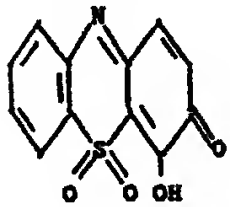
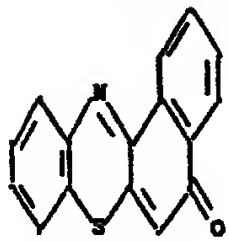
Test No.	Compound	Method of Administration	Ed_{50}
A		i.p.	0.5 mg/kg
B		p.o.	1.5 mg/kg
C		i.p.	about 5.0 mg/kg
D		p.o.	1.0 mg/kg
E		p.o.	37% inhibition at 1.5 mg/kg
F		p.o.	36% inhibition at 5 mg/kg

TABLE 6

PAF-induced Hyperalgesia Assay for Compound of Example 2

Experiment 1

	Vocalization Threshold[a]	% Inhibition
0.01 mg/kg p.o.	28.2 ± 5.2	40
0.03	40.2 ± 5.0	80
0.1	37.4 ± 3.9	80
0.3	45.4 ± 3.7	90
3.0	46.0 ± 3.0	100
Control	14.4 ± 1.6	

Experiment 2

	Vocalization Threshold[a]	% Inhibition
0.001 mg/kg p.o.	10.0 ± 1.6	0
0.003	16.4 ± 2.8	30
0.01	18.0 ± 2.9	30
0.1	29.6 ± 4.4	60
Control	11.2 ± 1.4	

[a] mmHg Mean ± S.E.M., n = 10 Reading taken 3 hr. after injection of PAF, (3.5 hr. after administration of compound).

TABLE 7

Rat Brewer's Yeast Hyperalgesia Assay for Example 2 Compound

Dose	Vocalization Threshold[a]	% Inhibition
0.3 mg/kg p.o.	17.6 3.1	30
1.0	19.4 3.1	30
3.0	30.0 5.8	60
10.0	28.6 3.0	70
30.0	32.6 3.3	80
Control	10.2 1.3	

[a] mmHg: mean ± S.E.M. n = 10

The test results presented above show that representative compounds of Formula I inhibit the mammalian biosynthesis of leukotrienes especially via the 5-Lipoxygenase pathway of arachidonic acid metabolism and have representative pharmaceutical utility e.g., for asthma, pain and allergy.

The pharmecautical compositions of the present invention will contain sufficient compound of Formule I in a dosage form suitable for inhibiting the mammalian biosynthasia of leukotrienes or, for the treatment desired. The effective concentration of the Formula I compound in the composition will vary as required by the mode of administration, dosage form and pharmacological effect and level desired. A general daily dosege of Formula I will range from 10 µg to 20 mg/kg of body weight. This dosage may be adminiatered in single or divided individual doses. More or less of the general daily dosage may be necessary depending upon the individual needs of the patient.

For treeting pulmonary conditions such as esthma, the mode of administration mey be oral, paranteral, by inheletion, or by auppository. Suitable oral dosage forma are tablata, elixirs, emulsions, solutions and capsules, including delayed or sustained release capsules. Parenteral dosage forms include solutions and emulsions. Dosage forms for administration by inhalation include sprays and aerosols. Thase inheletion formulations may be administered in metered doses renging from 0.1 µg to 200 µg, administered as needed.

For treeting allergies or allergic reactions, such aa allergic conjunctivitis and allergic rhinitis, the Formula I compound may be edministered by any conventional moda, eg., orally, parenterally, topically, subcutaneously or by inhaletion. The oral and parenteral dosage forms are tha same type as for the pulmonary treatment. Tha topical application dosage forms include ointments, selves, controlled-relaeaa patches, emulaions, solutions, thixotropic formulations, powders and sprays. For topical epplication, the percent by weight ectlve ingradient (Formula I compound) may vary from 0.001 to 10%.

For treating Inflammation the mode of administration may be oral, parenteral or by suppository. The varloua dosage forms are the aame as those described above.

For treating skin diseaaea such ea psoriaaia and atopic darmatitis, oral, topical or parenteral administretion ia useful. For topical applicetion to the diseases area selvea, patchea, controlled releese patchea and emuleions are convenient dosage forms.

For uaa aa an analgasic, i.e., for treating paln, any aultable moda of administration may ba uaad, a.g., oral, parenteral, by insufflation or by suppoeitory.

For treating cardiovascular conditions such as angina pectoris, any suitable mode of administration, e.g. oral, parenteral, topical or by inauffiation, and dosage form, e.g. pills, liquid formulations, controllad releasa capaules or controllad ralaase skin patches, may be uaed.

In addition to the common dosage forms aet out ebova, the compound of Formula I may alao ba administered for tha varioue utilitiee end indicatons or for inhibiting laukotriene syntheaia by controlled releaaa meana and/or dalivery devices auch as those deacribed in U.S. Patent Specifications US—A—3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Dosage forms for application to treat the eye are also disclosed in U.S. Patant Specification US—A—4,348,398.

In preparing aultable dosage forms, conventionel compounding procedurea and ingradients a.g. diluenta or carriers, may be used. The following are examples of representative pharmacautical dosaga forms:

Injectible Suspension	mg/mL
Compound of Exampie C	1—100
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Methyl paraben	1.8
Propyl paraben	0.2
Weter for injection to a total volume of 1 ml	

Aerosol for Oral Inhibition	mg/can (200 doses/can)
Compound of Formula I	2—40
Oleic Acid	0.2—4.0
Trichloromonofluoro methane	5,000—8,000 To a total
Dichloromonofluoro methane	15,000—12,400 of 20,400

Cream	mg/g
Compound of Formula I	1—100
Cetyl alcohol	130.0
Sodium Lauryl Sulfate	15.0
Propylene Glycol	100.0
Methyl paraben	1.8
Propyl paraben	1.2
Purified Water of sufficient quantity to make total 1 g	

Ointment	mg/g
Compound of Formula I	1—100
Methyl paraben	1.8
Propyl paraben	1.2
Petrolatum of sufficient quantity to make total 1 g	

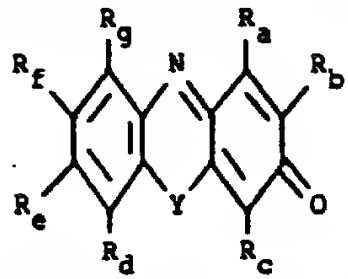
Tablet	mg/tablet
Compound of Formula I	0.2—350
Microcrystalline Cellulose	0—349.8
Povidone	14.0
Microcrystalline Cellulosa	90.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsula	mg/capsula
Compound of Formula I	0.2—350
Lactose Powder	248.5—598.3
Magnesium Stearate	1.5
	600

In addition to the compounds of Formula I, the pharmaceutical compositions can also contain other active ingredients, such as non-steroidal anti-inflammatory agents e.g. indomethacin, ibuprofen, sulindac and fenbufen, peripheral analgesic agents such as zomepirac and diflunisal, or cyclooxygenase inhibitors. Thay may also contain laukotriene antagonists such as those disclosed in European Patent Specifications EP—A—0,106,565, EP—A—0,104,885, EP—A—0,056,172 and EP—A—0,061,800 and in U.K. Patent Specification GB—A—2,058,785. These pharmaceutical compositions may also contain as the second active ingredient, antihistaminic agents such as benadryl, dramamine, histadyl and phenergan. Alternatively, they may include prostaglandin antagonists such as those disclosed in EP—A—0,011,067 or thromboxana antagonists such as those disclosed in US—A—4,237,160. The compounds of Formula I may also be advantageously combined with an H_1 or H_2-receptor antagonist, such as for instance cimetidine, ranitidine or terfanadine, or those disclosed in US—A—4,283,408; 4,362,736 and 4,394,508; and EP—A—0,040,696. These pharmaceutical compositions containing Formula I compound and a second

active ingredient are another embodiment of the present invention. The weight ratio of the Formula I compound to the second active ingredient may be varied and may range from 10:1 to 1:10.

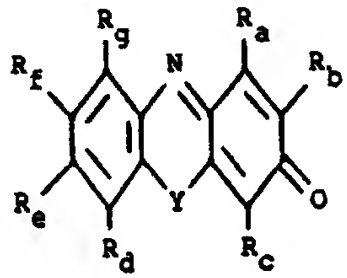
Another embodiment of the present invention are novel compounds encompassed by Formula I. These compounds have the Formula:



Tables 8 and 9 describe the novel compounds of the present invention:

TABLE 8

Novel Formula I Compound



Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	SCH_3	H	H	H	H	H
S	H	H	SCF_3	H	H	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	O-benzyl	Cl	H	H	H	H

TABLE 8 continued

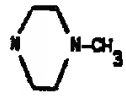
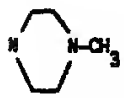
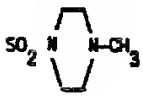
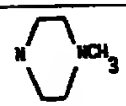
Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	OEt	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	h	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	CH_3	I	H	H	H	h
SO_2	H	H	OH	H	H	H	H
SO_2	H	OMe	OH	H	OMe	H	H
SO_2	OMe	OMe	Me	H	H	H	H
SO_2	H	H	OMe	H	H	H	H
SO_2	H	OMe	OM	H	OMe	H	H
S	OCH_3	OCH_3	Me	H	H	H	H
S	H	H	$COCH_3$	H	H	H	H
S	OCH_3	H	Br	H	OCH_3	H	H
S	OCH_3	Cl	Cl	H	OCH_3	H	H
S	OCH_3	H	Cl	H	OCH_3H	H	H
S	H		H	H	OCH_3	H	H
S	H		Br	H	OCH_3	H	H
SO_2	H	OCH_3	OH	H	OCH_3	H	H
SO_2	NHPr	H	NHPr	H	H	H	H
SO_2		H		H	H	H	H

TABLE 8 continued

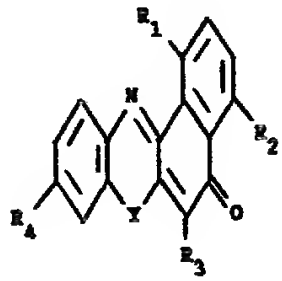
Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
SO_2	H	OCH_3		H	OCH_3	H	H
SO_2	H	OCH_3	Br	H	OCH_3	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	N	NHPr	H	OCH_3	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH_3	H	H
S	H	OCH_3	NH_2	H	OCH_3	H	H
S	H	OCH_3	NHPr	H	OCH_3	H	H
SO_2	H	OCH_3	NHPr	H	OCH_3	H	H
O	OCH_3	H	Cl	H	OCH_3	H	H
O	OCH_3	H	Br	H	OCH_3	H	H
O	NHPr	H	NHPr	H	H	H	H
SO_2	H	OCH_3	CN	H	OCH_3	H	H
SO_2	H	OCH_3	$NHCH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	S-N-Bu	H	OCH_3	H	H
SO_2	H	OCH_3	$CH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	SO_2CH_3	H	OCH_3	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H
S	H	CH_3	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF_3	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe_2	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO_2Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H
S	H	OMe	Br	H	Me	H	H

* R is H or C_1—C_4 alkyl.

Table 9 describes the novel compounds of the present invention having four rings.

TABLE 9

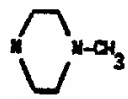
Novel Compounds of Formula II



II

Y	R_1	R_2	R_3	R_4
S	H	H	S-n-CH_4H_9	H
S	OH	H	CH_3	H
S	OCH_3	H	CH_3	H
S	H	H	F	H
S	H	H	CF_3	H
S	H	H	Cl	CF_3
S	H	H	Cl	SCH_3
S	H	H	Br	Cl
S	H	H	CH_3	Br
S	H	H	F	Br
S	H	H	$COCH_3$	Cl
S	H	H	CF_3	CH_3
S	H	H	S-n-C_4H_9	CH_3
S	H	H	CF_3	Cl
S	H	H	Cl	*CH_2COOR
S	H	H	Cl	*$CH(Me)CO_2R$
S	H	H	Cl	$COCH_3$
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF_3
S	H	H	H	CH_3
S	H	H	H	CH_2OH

TABLE 9 continued

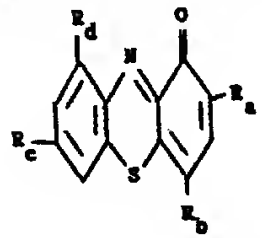
Y	R_1	R_2	R_3	R_4
S	H	H	H	OCH_3
S	H	H	H	SCH_3
S	H	H	H	*COOR
S	H	H	H	$*CH_2CO_2R$
S	H	H	H	$*CH(Me)CO_2R$
SO_2	H	H	NHPr	H
SO_2	H	H		H
SO_2	H	H	NH_2	H
SO_2	H	H	NHPr	OCH_3
S	-1,4-dihydro-		H	
S	H	H	NHPr	OCH_3
O	H	H	Cl	H
O	H	H	Br	H
O	H	H	Br	OCH_3
O	H	H	NHPr	OCH_3

*R is H or C_{1-4}alkyl.

Table 10 describes additional novel compounds of the present invention.

TABLE 10

Novel Compounds of Formula III

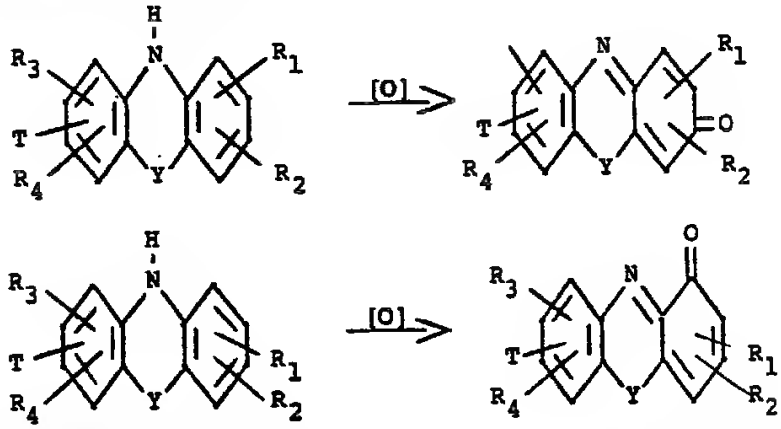


III

R_a	R_b	R_c	R_d
t-Bu	t-Bu	H	h
t-Bu	t-Bu	F	H
t-Bu	t-Bu	Me	H
t-Bu	t-Bu	SMe	H
t-Bu	t-Bu	H	OMe

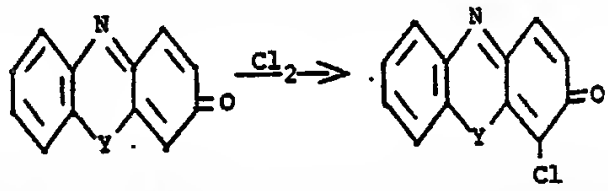
Formula I includes both novel and known compounds. These compounds may be prepared by any process available to the skilled artisan.

One such process for compounds where X = 0 involves the oxidation of the appropriata phenothiazine as illustrated by the following equations.

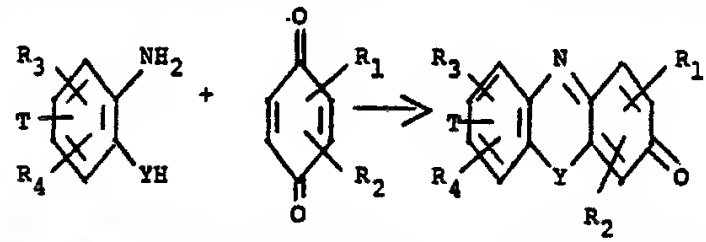


Various oxidizing agents end systems are taught in the art, e.g. PbO_2, HNO_3, $K_2Cr_2O_7$, $K_2Cr_2O_7$, Iodine or $FeCl_3$.

Another process useful for preparing some Formula I compounds containing halogen substituents is by direct haloganation of an appropriate phenothiazone or enelog thereof as illustrated by the following equation.

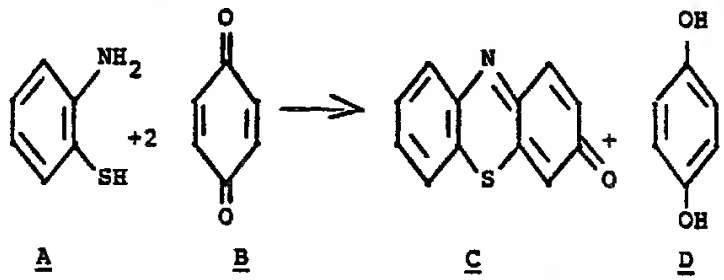


Still another process useful for preparing many of the Formule I compounds is by the reaction of an appropriate eniline with en appropriate quinone as illustrated by the following equation:



This general process is described in the literature.

A specific process for praparing the intermediate phenothiazin-3-one is illustratad by the following equation:



The process requires the use of 2 moles of quinone per mole of aniline. Any suitable solvent may be used. Example of such solvents are acetic acid, lower alkanols, acetic acid/H_2O, loweralkanol/water or other polar solvents. A preferred solvent is one which will dissolve *A*, *B* and *D* and in which *C* is substantially insoluble.

The reaction is readily carried out at room temperature — lower temperatures, e.g. as low as −10°C, may be used — elevated temperatures mey also be used but are not required. This process is more fully described in Europeen Patent Specification EP—A—0,149,297.

Another useful process to prepare certain of the compounds of the present invention is the oxidation of certain phenothiazines or benzo[a]phenothiazines by standard oxidizing agents such es potassium dichromete, $NaClO_2$ and 2-3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Severel of these benzo[a]phenothiazines and phenothiazines are described in EP—A—0,138,481 and EP—A—0,136,893.

Examples of the Formulae I and II compounds follow. These examples are illustretive and ere provided as en aid to understand the invention. All temperatures are in degrees Celsius and are uncorrected.

Example 1

Method A:

3H-Phenothiazin-3-one

To a stirred suspension of 1.72 kg (16 mol) of *p*-benzoquinone in 13 litres MeOH et room tempereture wes added slowly a solution of 1.0 kg (8 mol) of 2-aminothiophenol in 600 mol MeOH over a period of 1 hour. The resulting red mixture was stirred at room temperature for another 2 hours and then the product 3H-phenothiez-3-one wes filtered off. This 3H-phenothiazin-3-one was washed thoroughly with methanol and dried to give 1.07 kg of 3H-phenothiazin-3-one (61.49% yield), m.p. 157—159°C.

Method B:

To a stirring solution of 1.1 kg of ceric ammonium nitrate in 12.5 liters of H_2O and 1.25 liters of HOAc at 10°C was added dropwise a solution of 100 g of phenothiazine in 500 ml acetone over a period of 20 minutes. The resulting mixture wes stirred for another 20 minutes and the product 3H-phenothiezin-3-one was then filtered off. The filtered 3H-phenothiazin-3-one was washed with water thoroughly and dried to give 92 g of crude 3H-phenothiezin-3-one. The crude 3H-phenothiazin-3-one was extracted with minimum volume of CH_2Cl_2. Upon dilution of the CH_2Cl_2 solution with 10 timea the volume of cyclohexane, a precipitate was formed which wes filtered and dried to efford 35 g of 3H-phenothiazin-3-one.

Example 2

4-Chloro-3H-phenothiazin-3-one

To a stirring solution of 500 g (2.34 mol) of 3H-phenothiazin-3-one in 12.5 liters of glacial acetic ecid waa added 1.25 kg of potaasium dichromate. The mixture was atirred at room temperature for 1/2 hour. To this reaulting mixture waa then added 2.34 mol of a 1 M solution of chlorine in glacial acetic acid dropwiae over a period of 4 hours. The progress of the reection was monitored by tlc to enaure no exceaa chlorine was added. Aftar addition of chlorine waa completed the mixture waa stirred at room tamperatura for another 1/2 hour and was then poured into 120 liters of H_2O with vigorous atirring. The 4-chloro-3H-phenothiazin-3-one precipitated was allowed to settle overnight. The majority of the aqueoua solution was alphoned and discarded and the rest waa filtered. The filtered precipitate wes waahed thoroughly with weter and then rinaed with methanol end was allowed to dry to give 504 g crude 4-chloro-3H-phenothiazin-3-one which wes recryatellized from toluene, m.p. 221°.

Exemple 3

4-Chloro-2,7-dimethoxy-3H-phenothiezin-3-one

Following the procedure described in Example 2 but substituting 2,7-dimethoxy-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtelned, m.p. 264°C.

Analyais, calculated:	C, 54.63;	H, 3.27;	N, 4.55;	S, 10.42;	Cl, 11.52.
Observed:	C, 54.64;	H, 3.31;	N, 4.53;	S, 10.60;	Cl, 11.69.

Example 4

4-Chloro-1,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 1,7-dimethyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one for 3H-phenothiazin-3-one the title compound was obtained, m.p. 215—218°C.

Analysis, calculated:	C, 60.98;	H, 3.66;	N, 5.08;	S, 11.63;	Cl, 12.86.
Observed:	C, 60.78;	H, 3.75;	N, 4.99;	S, 11.79;	Cl, 13.01.

Example 5

4-Chloro-2,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Exemple 2 but substituting 2,7-dimethyl-3H-phenothiezin-3-one for 3H-phenothiazin-3-one the title compound was obtained, m.p. 193—195°C.

Analysis, calculated:	C, 60.98;	H, 3.66;	N, 5.08;	S, 11.63;	Cl, 12.86.
Observed:	C, 60.89;	H, 3.79;	N, 5.22;	S, 11.63;	Cl, 12.50.

Example 6

4-Chloro-2-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 2-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 206°C.

Analysis, calculated: C, 59.66; H, 3.08; N, 5.35; S, 12.25; Cl, 13.55.
Observed: C, 59.59; H, 3.35; N, 5.32; S, 12.64; Cl, 13.27.

Example 7

4-Chloro-7-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 7-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 218°C.

Analysis, calculated: C, 59.66; H, 3.08; N, 5.35; S, 12.25; Cl, 13.55.
Observed: C, 59.48; H, 3.17; N, 5.27; S, 12.40; Cl, 13.63.

Example 8

4-Chloro-7-ethoxy-2-methoxy-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 7-ethoxy-2-methoxy-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 236—239°C.

Analysis, calculated: C, 55.99; H, 3.76; N, 4.35; S, 9.96; Cl, 11.02.
Observed: C, 56.05; H, 3.93; N, 4.37; S, 10.11; Cl, 10.99.

Example 9

4-Bromo-2-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 2-methyl-3H-phenothiazin-3-one for 3H-phenothiazin-3-one and substituting bromine for chlorine, the title compound was obtained, m.p. 190°C.

Analysis, calculated: C, 50.99; H, 2.63; N, 4.57; S, 10.47; Br, 26.09.
Observed: C, 50.97; H, 2.69; N, 4.61; S, 10.56; Br, 26.24.

Example 10

9-Methoxy-3H-phenothiazin-3-one

To a suspension of p-benzoquinone (3.0 g) in 15 ml methenol was added 2-amino-3-methoxythiophenol (2.2 g) dissolved in 10 ml methenol. The mixture was stirred at room temperature for 45 minutes and concentrated *in vacuo*. The residue was triturated with ether and filtered. The resulting dark solid was chromatographed on silica gel and eluted with EtOAc, to afford the desired compound, m.p. 206—207°.

Analysis, calculated: C, 64.16; H, 3.73; N, 5.76; S, 13.16.
Observed: C, 64.10; H, 3.83; N, 5.69; S, 13.40.

Example 11

7-Fluoro-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol, the title compound was obtained, m.p. 240°C.

Analysis, calculated: C, 62.33; H, 2.61; N, 6.06; S, 13.86; F, 6.21.
Observed: C, 62.26; H, 2.70; N, 6.05; S, 14.04; F, 8.06.

Example 12

4-Chloro-7-fluoro-3H-phenothiazin-3-one

Following the procedure described in Example 2 but substituting 7-fluoro-3H-phenothiazin-3-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 250—255°C.

Analysis, calculated: C, 54.25; H, 1.90; N, 5.27; S, 12.07; F, 7.15; Cl, 13.34.
Observed: C, 54.10; H, 2.01; N, 5.35; S, 12.20; F, 7.20; Cl, 13.50.

Example 13

7-Fluoro-2-methoxy-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol and substituting 2-methoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 252°C.

Analysis, calculated: C, 59.76; H, 3.08; N, 5.36; S, 12.27; F, 7.26.
Observed: C, 59.60; H, 3.11; N, 5.20; S, 12.17; F, 7.33.

Example 14

2,4-Dimethoxy-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2,6-dimethoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 193°C.

Analysis, calculated: C, 61.52; H, 4.06; N, 5.12; S, 11.73.
Observed: C, 61.37; H, 4.14; N, 5.16; S, 12.90.

Example 15

1,2-Dimethoxy-4-methyl-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2,3-dimethoxy-5-methyl-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 138°C.

Analysis, calculeted: C, 62.70; H, 4.56; N, 4.87; S, 11.16.
Observed: C, 62.72; H, 4.74; N, 4.92; S, 11.28.

Example 16

1,7-Dimethyl-3H-phenothiazin-3-one and 2,7-dimethyl-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-methylthiophenol for 2-amino-3-methoxythiophenol end substituting 2-methyl-p-benzoquinone for p-benzoquinone, a mixture of the title compounds were obteined. Chromatography on silica gel eluting with 10% EtOAc in CH_2Cl_2 efforded firstly 2,7-dimethyl-3H-phenothiezin-3-one, m.p. 177°C.

Anelysis, calculeted: C, 69.70; H, 4.60; N, 5.81; S, 13.29.
Observed: C, 69.51; H, 4.82; N, 5.78; S, 12.27,

and secondly, 1,7-dimethyl-3H-phenothiazin-3-one. m.p. 168—170°C.

Analysis, calculeted: C, 69.70; H, 4.60; N, 5.81; S, 13.29.
Observed: C, 69.59; H, 4.63; N, 5.80; S, 13.40.

Exemple 17

2,4-Dichloro-7-fluoro-3H-phenothiazin-3-one

Following the procedure described in Exemple 10 but substituting 2-emino-5-fluorothiophenol for 2-emino-3-methoxythiophenol end substituting 2,6-dichloro-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 256—258°C.

Anelysis, calculated: C, 48.02; H, 1.34; N, 4.68; S, 10.68; F, 6.33; Cl, 23.62.
Observed: C, 47.93; H, 1.42; N, 4.63; S, 10.75; F, 6.42; Cl, 23.80.

Exemple 18

1,4-Dichloro-7-fluoro-3H-phenothiezin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-fluorothiophenol for 2-amino-3-methoxythiophenol end substituting 2,5-dichloro-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 245—247°C.

Analysis, calculated: C, 48.02; H, 1.34; N, 6.33.
Observed: C, 48.20; H, 1.14; N, 6.20.

Example 19

2-Methoxy-7-methylthio-3H-phenothiazin-3-one

Following the procedure described in Example 10 but substituting 2-amino-5-methylthio thiophenol for 2-emino-3-methoxythiophenol and substituting 2-methoxy-p-benzoquinone for p-benzoquinone, the title compound was obtained, m.p. 222—224°C.

Anelysis, calculated: C, 58.11; H, 3.83; N, 4.84; S, 22.16.
Observed: C, 58.28; H, 4.24; N, 4.62; S, 22.02.

Example 20

4-Trifluoromethyl-3H-phenothiazin-3-one and 2,4-bis(trifluoromethyl)-3H-phenothiazin-3-one

A solution of 3H-phenothiazin-3-one (10 g), trifluoromethyl iodide (50 g) snd pyridine (40 ml) in scetonitrile (140 ml) was irradiated with a 450 watt lamp for 3 days. The volatiles were removed under vacuum and the resulting residue chromatographed on a silica gel column eluting with 5% EtOAc/CH_2Cl_2 to efford firstly, 2,4-bis(trifluromethyl)-3H-phenothiazin-3-one (650 mg) m.p. 173—175°C.

Analysis, calculated: C, 48.14; H, 1.44; N, 4.01; S, 9.18; F, 32.64.
Observed: C, 48.25; H, 1.72; N, 4.00; S, 9.28; F, 32.51.

Secondly, 4-trifluoromethyl-3H-phenothiazin-3-one (1.76 g), m.p. 184—185°C.

Analysis, calculated: C, 55.51; H, 2.15; N, 4.98; S, 11.40; F, 20.27.
Observed: C, 55.60; H, 2.14; N, 5.22; S, 11.43; F, 20.41.

Example 21

4-Acetyl-3H-phenothiazin-3-one

A solution of 3H-phenothiazin-3-one (2 g) and acetaldehyde (32 ml) in benzene (240 ml) was irradiated with a 450 watt lamp for 2 days. The volatiles were removed under vecuum end the residue chrometographed on e silica gel column eluting with 25% EtOAc/hexane to afford the desired compound, m.p. 222°C.

Analysis, calculated: C, 65.87; H, 3.55; N, 5.49; S, 12.56.
Observed: C, 65.88; H, 3.61; N, 5.30; S, 12.70.

Example 22

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one

Step 1:

2-Methoxy-p-benzoquinone

Vanillin (2.432 kg) was added to a solution of sodium hydroxide (640 g) in water (8 l) and cooled to 10°C with an ice-bath. Then a solution of hydrogen peroxide (30%) (2.4 l) was added at a rate to keep the temperature of the reaction mixture below 30°C. The addition completed (about 2 hours), the reaction mixture was added over a period of 3 hours to a suspension of sodium periodate (880 g) in water (4 l) and acetic acid (640 ml) cooled with an ice-bath to 10°C (the temperature of the reaction mixture was kept below 35°C). The precipitate was filtered, washed with cold water followed by ethanol/hexane (1:1) mixture and air-dried to afford the title compound (1.9 kg), m.p. 144—147°C.

Step 2:

2-Amino-5-methoxythiophenol

To a solution of potassium hydroxide 8N (1.3 l) was added 2-amino-6-methoxybenzothiazole (750 g) and the mixture was refluxed for 18 hours. The resulting solution was neutralized by the addition of concentrated HCl, to pH 8.0, then acetic acid to pH 6.0. The precipitate which formed was filtered and washed with water to afford the title compound which was used immediately in Step 3.

Step 3:

2,7-Dimethoxy-3H-phenothiazin-3-one

To a suspension of 2-methoxy-p-benzoquinone, (1.15 kg) (Step 1) in methanol (8 l) was added portionwise a suspension of 2-amino-5-methoxythiophenol (from Step 2) in methanol (6 l). The reaction mixture was stirred for 15 minutes at room temperature, filtered and the collected solid washed with methanol (8 l). The product isolated was swished with DMF (16 l) for 2 hours, filtered and air-dried. The crude material was dissolved in hot DMF (16 l) (130°—140°C), filtered through Celite® and the filtrate cooled to room temperature. The crystals were filtered, washed with methanol (8 l) and air-dried to afford the title compound (703 g), m.p. 237—238°C.

Step 4:

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one

A solution of bromine (280 g) in acetic acid (2.8 l) was added over a period of 30 minutes to a suspension of 2,7-dimethoxy-3H-phenothiazin-3-one (250 g) (Step 3) in acetic acid (7.5 l) and stirred for 2 hours. Methanol (12 l) was added and the mixture was stirred until the black suspension became an orange suspension. Then, the precipitate was filtered, washed with methanol and air-dried to afford the desired compound (312 g), m.p. 260—261°C.

Analysis, calculated: C, 47.74; H, 2.86; N, 3.98; S, 9.10; Br, 22.69.
Observed: C, 47.74; H, 2.81; N, 3.90; S, 9.02; Br, 22.37.

Example 23

4-Chloro-2-ethoxy-3H-phenothiazin-3-one and 4-chloro-2,7-diethoxy-3H-phenothiazin-3-one

Metallic sodium (506 mg) was dissolved in absorbed ethanol (75 ml) and 4-chloro-3H-phenothiazin-3-one (4.95 g) was added and stirred overnight at room temperature. The solvent was removed in vacuo, the resulting residue stirred in acetone (500 ml) for 1 hour and filtered. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column eluting with 5% EtOAc/toluene to afford firstly, 4-chloro-2-ethoxy-3H-phenothiazin-3-one (1.33 g), m.p. 188—189°C.

Analysis, calculated: C, 57.63; H, 3.45; N, 4.80; S, 10.99; Cl, 12.15.
Observed: C, 57.66; H, 3.54; N, 4.81; S, 11.16; Cl, 12.02.

and secondly, 4-chloro-2,7-diethoxy-3H-phenothiazin-3-one (110 mg), m.p. 227—228°C.

Analysis, calculated: C, 57.22; H, 4.20; N, 4.17; S, 9.55; Cl, 10.56.
Observed: C, 57.19; H, 4.35; N, 4.07; S, 9.62; Cl, 10.61.

Example 24

2-(n-Butylthio)-3H-phenothiazin-3-one

To a solution of 3H-phenothiazin-3-one (0.64 g) in 75 ml methanol was added thiethylamine (1.0 ml) and n-butanethiol (0.58 ml). The mixture was stirred at room temperature for 48 hours. Then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.67 g) was added. The mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was chromatographed on neutral alumina (Act III) and eluted with 15% EtOAc/hexane to afford the title compound (0.4 g), m.p. 133°C.

Analysis, calculated: C, 63.78; H, 5.02; N, 4.65.
Observed: C, 63.61; H, 5.04; N, 4.51.

Example 25

4-(n-Butylthio)-3H-phenothiazin-3-one

To a solution of phenothiazin-3-one (0.21 g) in 20 ml THF was added triethylamine (0.28 ml) and n-butanethiol (0.2 ml). The mixture was refluxed for 15 hours and then cooled to room temperature. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.22 g) was added and the reaction wes stirred for 2 hours at 25°. The solvent was removed *in vacuo*. The residue was chromatographed on neutral alumina (Act III) and eluted with 15% EtOAc/hexane to afford the title compound, m.p. 72°C.

Analysis, calculated: C, 63.78; H, 5.02; N, 4.05; S, 21.24.
Observed: C, 63.83; H, 5.07; N, 4.86; S, 21.06.

Example 26

4-(n-Butylthio)-2-methyl-3H-phenothiazin-3-one

To a solution of 2-methyl-phenothiazin-3-one (0.23 g) in 12 ml dichloroethane was added triethylamine (0.8 ml) and n-butanethiol (0.7 ml). The mixture was stirred at room temperature for 72 hours. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.22 g) was added. The mixture was stirred et room temperature for 2 hours. The mixture wes stirred et room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was chromatographed on neutral alumina (Act III) eluting with 15% EtOAc/hexane to give the title compound (120 mg), m.p. 97°C.

Analysis, calculated: C, 64.75; H, 5.43; N, 4.44.
Observed: C, 64.62; H, 5.53; N, 4.43.

Example 27

2-S-Glutathionyl-3H-phenothiazin-3-one

A mixture of phenothiazin-3-one (0.22 g), triethylamine (0.41 ml) and glutathione (0.3 g) in 1,2-dichloroethene (12 ml) wes stirred at room temperature for 5 days. The solvent was removed *in vacuo*. The residue was dissolved in water and filtered. The filtrate was concentrated *in vacuo* and then chromatographed on XAD resin and eluted with water to give the title compound.

Example 28

4-Chloro-2-S-glutathionylphenothiazin-3-ona

Following the procedure of Example 27, but substituting 4-chloro-3H-phenothiazine-3-one for 3H-phenothiazin-3-one, the title compound wea obtained.

Example 29

5H-Benzo[a]phenothiazin-6-one

Following the procedure described in Example 10 but subatituting 2-aminothiophenyl for 2-amino-3-methoxythiophenyl and substituting 1,4-naphthoquinone for p-benzoquinona the title compound wea obtained, m.p. 176—177°C.

Example 30

6-Chloro-5H-benzo[a]phenothiazin-5-one

Following the procedure described in Example 2, but substituting 5H-benzo[a]phenothiazin-5-one for 3H-phenothiazin-3-one, the title compound was obtained, m.p. 230—231°C.

Example 31

6-Methyl-5H-benzo[a]phenothiazin-5-one

Following the procedure described in Example 10, but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 2-methyl-1,4-naphthoquinone for p-benzoquinone, the title compound was obtained, m.p. 181°C.

Analysis, calculated: C, 73.62; H, 4.00; N, 5.05; S, 11.56.
Observed: C, 73.77; H, 4.16; N, 4.99; S, 11.69.

Example 32

1-Hydroxy-6-methyl-5H-phenothiazin-5-one

Following the procedure described in Example 10 but substituting 2-aminothiophenol for 2-amino-3-methoxythiophenol and substituting 5-hydroxy-2-methyl-1,4-naphthoquinone for p-benzoquinone, the title compound was obtained, m.p. 226—228°C.

Analysis, calculated: C, 69.61; H, 3.78; N, 4.77; S, 10.93.
Observed: C, 69.66; H, 3.90; N, 4.66; S, 10.77.

Example 33

1-Methoxy-6-methyl-5H-phenothiazin-5-one

Potassium *tert.*-butoxide (500 mg) was added to a suspension of 1-hydroxy-6-methyl-5H-benzo[a]phenothiazin-5-one (from Example 32) (500 mg) and methyl iodide (2 ml) in DMF (20 ml). After 30 minutes at room temperature, EtOAc (250 ml) was added followed by water (200 ml). The aqueous layer

was decanted and the organic layer was dried and evaporeted to dryness. The residue was treated with ether, filtered and air-dried to afford the desired product (420 mg), m.p. 170—171°C.

Analysis, calculated: C, 70.34; H, 4.26; N, 4.56; S, 10.43.
Observed: C, 70.37; H, 4.44; N, 4.45; S, 10.52.

Example 34

4-Hydroxy-3H-phenothiazin-3-one-5,5-dioxide

To a suspension of 3-hydroxy-10H-phenothiazine-5,5-dioxide (1.75 g, 7 mmoles) in 2% aqueous sulfuric acid (25 ml) there was added, at room temperature, a solution of 80% sodium chlorite (3.17 g, 28 mmoles) in water (25 ml). The mixture was stirred for 15 minutes, then the red-orange precipitate was filtered to afford crude product (1.73 g). Purification was achieved by crystallization from DMF-methanol, m.p. 266° (dec.).

Analysis, calculated: C, 55.16; H, 2.70; N, 5.36; S, 12.27.
Observed: C, 54.68; H, 2.76; N, 5.38; S, 12.47.

Example 35

4-Chloro-3H-phenoxazin-3-one

To a solution of 1.2 g of 3H-phenoxazin-3-one in acetic acid (25 ml) waa added $K_2Cr_2O_7$ (3.7 g). A solution of chlorine in acetic acid was added dropwise to the resulting suspension. After disappearance of the starting material, as monitored by TLC, the reaction mixture waa poured into 200 ml of H_2O and the resulting precipitate was filtered (1.2 g) and chromatographed on silica gel to yield the title compound.

Analysis, calculated: C, 62.22; H, 2.61; Cl, 15.30.
Obsarved: C, 62.10; H, 2.75; Cl, 15.24.

Example 36

2,4-Di-t-butyl-1H-phenothiazin-1-one

To a solution of 4.4 gm of 3,5-di-t-butyl-1,2-benzoquinona in 20 ml of ethar was added a aolution of 1.25 g of 2-aminothiophanol in 5 ml of ether. After stirring for 1 hour at 25°, tha reaction mixture was evaporated. The residue was purified by flash chromatography on silica gel using 2% ethyl acetate in benzene as eluant. There was thus obtained 860 mg of the title compound as dark blua plates, m.p. 137—141°.

Analysis, calculatad: C, 73.81; H, 7.12; N, 4.30; S, 9.85.
Observed: C, 73.77; H, 7.33; N, 4.33; S, 9.85.

Example 37

4-Bromo-1,7-dimethoxy-3-H-phenothiazin-3-one

To a auspansion of 1,7-dimethoxy-3H-phanothiazin-3-one (300 mg) in acetic acid (9 ml) waa added a 0.63 M aolution of Br_2 in acetic acid (1.92 ml). After 15 minutea, mathanol waa added and the aolid filtered, washed with ether and air dried to afford the title compound (353 mg), m.p. 267—270°C (dec).

Example 38

4-Chloro-1,7-dimethoxy-3H-phenothiazin-3-one and 2,4-dichloro-1,7-dimethoxy-2-H-phenothiazin-3-one

To a suapension of 1,7-dimethoxy-3H-phenothiazin-3-one (800 mg) in acetic acid (24 ml) was addad a 1.15 M solution of Cl_2 in acetic acid (3.1 ml). After 15 minutes, methanol waa added and tha mixtura was filtered, washed with ether and air dried to afford a mixture of the two title compounds (700 mg), whlch were aeparated on a silica gel column (EtOAc:CH_2Cl_2, 1:9), affording 4-chloro-1,7-dimethoxy-2H-phenothiazin-3-one, m.p. 278—280°C (dec.)

Analysis, Calculated: C, 54.64; H, 3.28; N, 4.55; S, 10.42; Cl, 11.52.
Observed: C, 54.44; H, 3.26; N, 4.62; S, 10.54; Cl, 11.48.

and 2,4-dichloro-1,7-dimethoxy-3H-phenothiazin-3-one, m.p. 259—260°C (dec.) m/e 341.

Example 39

7-Methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one

A mixture of 7-methoxy-3H-phenothiazin-3-one (1.2 g) and N-methyl piperazine HCl (3.4 g) in DMF (20 ml) was heated at 100°C for 3 hours. Then $NaIO_4$ (1 g) was added and the reaction mixture was heated at 100°C for 1 hour. Ice-water was added to the reaction mixture followed by ethyl acetate. The aqueous layer was dacanted, filtered and the filtrate basified with K_2CO_3 and extracted with ethyl acetate. The organic layer was evaporated to dryness, the resulting residue was dissolved in CH_2Cl_2, dried and evaporated to dryness to afford the crude final product (1.2 g) which was purified by chromatography on silica gel column eluting with 10% MEOH/CH_2Cl_2 to give the title compound, m.p. 208—209°.

Example 40

4-Bromo-7-methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one

To a suspension of 7-methoxy-2-(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one (500 mg) in acetic acid (10 ml) was added a solution of bromine in acetic acid (0.5 M) (6 ml) and stirred for 5 minutas. Hexane

(100 ml) was added and the resulting precipitate was filtered. The solid was suspended in a mixture of aqueous K_2CO_3 (50 ml), EtOAc (100 ml) and methanol (20 ml) and stirred for 15 minutes. After filtration and decantation, the organic layer was washed with brine, dried and evaporated to dryness to afford the title compound (190 mg) m.p. 209—210° (dec.).

Example 41

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

Step 1:

4-Bromo-3-hydroxy-2,7-dimethoxy-10-H-phenothiazine

To a suspension of 4-bromo-2,7-dimethoxy-3H-phenothiazin-3-one (100 g) in a mixture of ethylacetate (2 l) and water (1 l) was added sodium hydrosulfite (200 g) in one batch with mechanical stirring. The orange reaction mixture was stirred for 15 hours under a nitrogen atmosphere. The resulting white reaction mixture was filtered and the precipitate washed with water under a nitrogen atmosphere to prevent air oxidation of the compound. The title compound (130 g) was obtained as a wet material and was used as such in the next step (Step 2). An analytical sample was air dried, m.p. 185°C.

Analysis, Calculated: C, 47.74; H, 3.42; N, 3.95; S, 9.05; Br, 22.56.
Observed: C, 47.21; H, 3.39; N, 3.74; S, 8.76; Br, 22.44.

Step 2:

3-Acetoxy-4-bromo-2,7-dimethoxy-10-H-phenothiazine

Wet 4-bromo-3-hydroxy-2,7-dimethoxy-10-H-phenothiazine (130 g) (from step 1) was suspended in pyridine (230 ml). The mixture was cooled to 0°C in an ice-water bath. Acetic anhydride (195 ml) was then slowly added. The solution was left stirring at room temperature for 1/2 hour. The mixture was then concentrated under reduced pressure to approximately 1/3 of the original volume. Then a mixture of ether:hexane, 1:1 (700 ml) was added, causing a large amount of crystals to appear. These crystals were filtered, washed with ether, and air dried, giving 51.4 g of pure 3-acetoxy-4-bromo-2,7-dimethoxy-10-phenothiazine. The mother liquors were reevaporated, and ether and hexane were added again, giving 36.37 of crude 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine m.p. 201—203°C.

Analysis, Calculated: C, 48.50; H, 3.56; N, 3.53; S, 8.09.
Observed: C, 48.31; H, 3.47; N, 3.47; S, 8.00.

Step 3:

3-Acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide

To 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazin (20 g) (from Step 2) in suspension in CH_2Cl_2:MeOH, (1:1) (500 ml), was added m-chloroperoxybenzoic acid (26.0 g). The reaction mixture rapidly became deep brown with the formation of a yellowish precipitate which corresponded to the intermediate sulfoxide on the 5-position. The mixture was heated at reflux for 18 hours. The solid was then filtered and washed with ether. Since there was still some sulfoxide remaining, the solid was suspended in ethanol:1,2-dichloroethane (500 ml) with 1.35 g of m-chloroperoxybenzoic acid and heated at reflux overnight (15 hours). The solid was then filtered and washed with ether and air dried giving 13.0 g of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide, m.p. 260°C.

Analysis, Calculated: C, 44.87; H, 3.29; N, 3.27; S, 7.49.
Observed: C, 44.82; H, 3.21; N, 3.18; S, 7.67.

Step 4:

4-Bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide

To a suspension of 3-acetoxy-4-bromo-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (10.0 g) in methanol (105 ml) was added a solution of 2N aqueous sodium hydroxide (74 ml) under a nitrogen atmosphere. After 20 minutes, the mixture was acidified with 10% v/v aqueous acetic acid (250 ml), causing a large amount of compound to precipitate. The mixture was then diluted with water (105 ml) and the solid filtered, washed with water and ether and dried in a desiccator to afford quantitatively the title compound, m.p. 252—260°C (dec).

Step 5:

4-Bromo-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazin-5,5-dioxide (from Step 4) (1 g) in THF (10 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.17 g). After 15 minutes, the mixture was filtered, the solid washed with ether and air dried. The solid was filtered through a silica gel pad with CH_2Cl_2:EtOAc, 1:1, to afford the title compound (300 mg), m.p. 228—230°C (dec), m/e 383.

Example 42

2,7-Dimethoxy-4-(4-methylpiperazin-1-yl)-3H-phenothazin-3-one-5,5-dioxide

To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (1 g) in THF (10 ml) was added 2,3-dichloro-5,5-dicyano-1,4-benzoquinone (1.17 g). After a period of 20 minutes, N-methyl piperezine (1.44 ml) was slowly edded. After 20 minutes, hexane was added to the mixture and the resulting precipitate was filtered, washed with ether and air dried. The compound was chromatographed using CH_2Cl_2:MeOH (9.5:0.5) as eluant, to afford the title compound (242 mg), m.p. 261°C (dec.).

Analysis; Calculated: C, 58.67; H, 5.83; N, 10.80; S, 8.24.
Observed: C, 58.73; H, 5.67; N, 10.83; S, 8.56.

Example 43

4-Hydroxy-2,7-dimethoxy-3H-phenothiazin-3-one-5,5-dioxide

To a stirred suspension of 4-bromo-3-hydroxy-2,7-dimethoxy-10H-phenothiazine-5,5-dioxide (100 mg) in THF (10 ml) was added weter (0.1 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.12 g). After 20 minutes, hexene was added and the solid was filtered, washed with ether and air dried to efford the title compound, m.p. 333—335°C (dec.).

Example 44

1,4-Bis(1-propylemino)-3H-phenothiazin-3-one-5,5-dioxide

To a solution of 3-hydroxy-10H-phenothiazine-5,5-dioxide (989 mg) in THF (50 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.82 g). The resulting green mixture was stirred at room temperature for 3 minutes, then there was added n-propyl amine (2.36 g). The mixture was stirred for 20 minutes and then filtered. The filtrate was evaporated to dryness and the residue chromatographed on a column of silica gel eluting with e 1:20 mixture of ethyl acetate and dichloromathane to efford the title compound as a purple solid (850 mg). Crystallization from methane afforded purple crystals (608 mg), m.p. 174—176°C.

Analysis, Calc'd: C, 60.14; H, 5.89; N, 11.69; S, 8.92.
Found: C, 80.08; H, 5.93; N, 11.80; S, 8.71.

Example 45

1,4-Bis(4-methylpiperazin-1-yl)-3H-phenothiazin-3-one-6,6-dioxide

The procedure of Example 44 was used, substituting N-methyl piperazine for n-propyl amine to afford the title compound. It was crystallized from e toluene-hexane mixture to afford red crystals, m.p.: 247—249°C (dec.).

Analysis, Calc'd: C, 59.84; H, 6.16; N, 15.86; S, 7.26
Found: C, 69.98; H, 6.36; N, 15.58; S, 7.1.

Example 46

6-(1-Propylamino)-5H-benzo[a]phenothiazin-5-one-7,7-dioxida

Step 1: 6-acetoxy-12H-benzo[a]phenothiazine

To a stirred solution of 5-hydroxy-12H-benzo[e]phenothiazine (50 g) in pyridine (116 ml) was edded ecetic anhydride (48 ml). The reaction was exothermic stirring was continued without cooling for 30 minutes, then the mixture wes cooled to 10°C using an ice bath. The yellow crystalline solid was filtered and washed with ether to afford the title compound (23.4 g). The product was crystallized from ethyl acetate, m.p. 185—186°C.

Step 2: 5-acetoxy-12H-benzo[a]phenothiazine-7,7-dioxide

To a suspension of 5-acetoxy-12H-benzo[a]phenothiazine (10 g) in dichloromethane (125 ml), was added a solution of m-chloroperoxybenzoic acid (18 g) in methenol (125 ml). The mixture was refluxed for 2.5 hours, then after cooling to room temperature the insoluble solid was filtered to afford the desired sulfone (8.6 g). The solid wes recrystallized from THF m.p. 284—287°C.

Analysis, Calc'd: C, 63.70; H, 3.86; N, 4.13; S, 9.45.
Found: C, 63.67; H, 3.82; N, 4.20; S, 9.44.

Step 3: 5-hydroxy-12H-benzo[a]phenothiazine-7,7-dioxide

To a suspension of 5-acetoxy-12H-benzo[a]phenothiezine-7,7-dioxide (6.6 g) in methanol (200 ml), kept under a nitrogen atmosphere was edded 2N aqueous sodium hydroxide solution (132 ml). The mixture was stirred at room temperature for 7 minutes, then there was added 10% acetic ecid (200 ml) and water (300 ml). After 10 minutes of stirring the mixture was filtered to afford the title compound (5.68 g) as a pink solid. The solid was recrystallized from THF, m.p. 334°C (dec).

Analysis, Calc'd: C, 63.70; H, 3.86; N, 4.13; S, 9.45.
Found: C, 63.67; H, 3.82; N, 4.20; S, 9.44.

Step 4: 6-(1-Propyl amino)-5H-benzo[a]phenothiezin-5-one-7,7-dioxide

To a suspension of 5-hydroxy-12H-benzo[a]phenothiazine-7,7-dioxide (594 mg) in THF (10 ml) was added 2,3-dichloro 5,6-dicyano-1,4-benzoquinone (1.021 gram). The mixture was stirred at room temperature for 2 minutes, then there was added n-propyl amine (0.2 ml). The stirring was continued for 0.5 hour, then the mixture was evaporated to dryness. To the residue was added 50 ml dichloromethane and the mixture was stirred for 15 minutes and filtered. The filtrate was evaporated to dryness and the residue crystallized from a mixture of toluene and hexane to afford the title compound (442 mg) as a red-brown crystalline solid, m.p. 149—151°C (dec.).

Analysis, Calc'd: C, 64.75; H, 4.58; N, 7.95; S, 9.10.
Found: C, 64.66; H, 4.48; N, 7.95; S, 9.04.

Example 47

6-(4-Methyl piperazin-1-yl)-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

The procedure of Example 46, Step 4 was used, substituting N-methyl piperazine for n-propyl amine, to afford the title compound, m.p. slow dec. from 183°C.

Analysis, Calc'd: C, 64.10; H, 4.87; N, 10.68; S, 8.15.
Found: C, 63.89; H, 4.90; N, 10.56; S, 8.10.

Example 48

6-Amino-5H-benzo[a]phenothiazin-5-one-7,7-dioxide

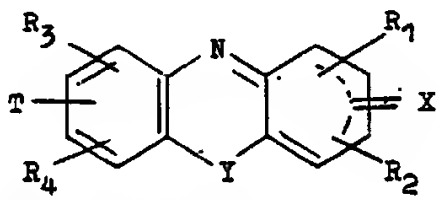
The procedure of Example 46, Step 4 was used, substituting 28% aqueous ammonium hydroxide solution for n-propyl amine, to afford the title compound, m.p. 264—266°C.

Certain of the compounds herein disclosed contain one or more centars of esymmetry. The present invention is meant to include the various diastereomers of such compounds as well es their racemic and optically activa resolved forms.

Some of the compounds described may exist in one or mora teutomeric forms. All such tautomeric forms are included within the present invention.

Claims

1. The use, for the manufacture of a medicament for inhibiting mammalian leukotriena biosynthesia or action, of a compound of the Formula i, a compound that ia a salt of a compound of the Formula I, or e pharmaceutical composition containing such a compound:



I

in which

X is in the 1 or 3 position end is O, S or NR;

R is H, C_{1-6} branched or iinear aikyi, CN or phenyl;

Y is O, Se, S, SO, SO_2 or NR; and the broken iine represents a doubie bond between the 1 end 2 or 2 and 3 positions;

each of R_1, R_2, R_3 and R_4 independently of the others, is

(1) hydrogen,

(2) C_{1-6} alkyl,

(3) C_{2-6} alkenyl,

(4) $-(CH_2)_nM$

where n is 0 or an integer from 1 to 6 and M is

(a) OR_5,

(b) helogen,

(c) CF_3,

(d) SR_5 where R_5 is H; C_1—C_6 alkyl; benzyi; phenyi or substituted phenyl where the substituents are C_{1-3} alkyl, halogen, CN, CF_3, $COOR_6$, CH_2COOR_6, $(CH_2)_nNR_8R_9$ where n is 0, 1 or 2, C_{1-3} alkoxy, OH or C_{1-6} haloalkyl; $-(CH_2)_mCOOR_6$, where m is 0 or an integer from 1 to 6 and R_6 is H, phenyl or C_{1-6} elkyl; CN, formyl, CF_3 or CH_2—R_{12}, where R_{12} is C_{1-5} alkyl, phenyi or dimethylamino;

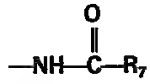
(e) phenyl or substituted phenyl as defined above for R_5;

(f) $COOR_6$;

(g) 

where R_{15} is H, $(CH_2)_n COOR_6$ where n is 0 or an integer from 1 to 4, C_{1-6} alkyl, CF_3, phenyl, or substituted phenyl as defined above for R_5;

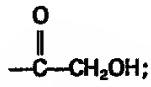
(h) tetrazole;

(i) 

where R_7 is C_{1-6} alkyl, benzyl or phenyl;

(j) $—NR_8R_9$ where R_8 and R_9 are independently selected from H, phenyl or substitutad phenyl as defined above for R_6 or C_{1-4} alkyl, C_{1-4} alkylaminoalkyl, or may be joined through the N to form a 4-methyl piperazinyl radical;

(k) $—NHSO_2R_{10}$ where R_{10} is OH, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl or CF_3;

(l) 

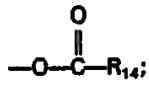
(m) $—SOR_{11}$ where R_{11} is C_{1-6} alkyl, phenyl or substituted phenyl as defined abova for R_5, $(CH_2)_mCOOR_6$ where m is 1 to 6, CN, formyl or CF_3;

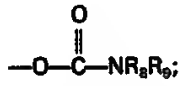
(n) $—CONR_8R_9$;

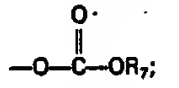
(o) $—SO_2NR_8R_9$;

(p) $—SO_2R_{13}$ where R_{13} is OH, H, C_{1-6} alkyl, phenyl or substituted phanyl es defined above for R_5, $(CH_2)_mCOOR_6$ where m is 1 to 6, CN or CF_3;

(q) NO_2;

(r) 

(s) 

(t) 

(u) —CN; or

(v) $NR_{15}R_{16}$ whare R_{15} and R_{16} are such that $NHR_{15}R_{16}$ is an essential emino acid;

or any two of R_1, R_2, R_3 and R_4 are joined to form a fourth saturated or unsaturated C_{5-6} ring; and

T is H, halogen or CF_3.

2. Tha usa claimad in Claim 1, in which, in Formula I, X is in the 1-position.

3. Tha use claimad in Claim 2, in which X is O or NR.

4. Tha use claimed in Claim 3, in which, in Formula I, Y is S, SO, SO_2, NR or O and, in the structural unit $(CH_2)_nM$, n is 0 or 1.

5. The use claimed in Claim 4, in which, in Formula I, X is O and Y is S.

6. The use claimed in Claim 1, in which, in Formule I X is in the 3-position.

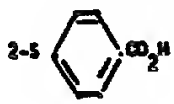
7. The use claimed in Claim 6, in which X is O or NR.

8. The use claimed in Claim 7, in which in Formula I Y is S, SO, SO_2, NR or O and in the structural unit $(CH_2)_nM$, n is 0 or 1.

9. The use claimed in Claim 8, in which Y is S or O.

10. The use claimed in Cleim 9, in which X is O and Y is S.

11. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of e compound of the Formula I, or e pharmeceutical composition containing such a compound, in which, in Formule I, the variables are as defined as follows, X being in the 1-position:

Y	X	R_1	R_2	R_3	R_4	T
O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
O	O	2-t-Bu	H	4-Me	H	H
S	S	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO or SO_2	O	2-Cl	H	H	H	H
"	O	2-SCF_3	H	H	H	H
"	O		H	H	H	H
S	O	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO or SO_2	O	2-CN	H	H	H	H
"	O	H	3-CO_2Et	H	H	H
"	O	H	3-Cl	H	H	H
"	O	H	H	4-Cl	H	H
"	O	H	H	4-SO_2CH_3	H	H
"	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N—CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	7-SO_2CH_3	H
S	O	2-Cl	H	4-SO_2CH_3	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	2-CF_3	H	H	H	H
S	O	2-SCF_3	H	H	H	H
S	O	2-SO_2CF_3	H	H	H	H
S	O	H	3-Cl	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
S	O	H	3-CO_2Et	H	H	H
S	O	H	3-CO_2H	H	H	H
S	O	H	3-CN	H	H	H
S	O	H	3-SCF_3	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	4-SCF_3	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	8-CO_2Et	H
S	O	2-Cl	H	H	8-CO_2H	H
S	O	2-Cl	H	H	8-CF_3	H
S	O	2-Cl	H	H	7-SO_2CH_3	H
S	O	H	3-$CONMe_2$	H	H	H
S	O	2-Cl	H	H	7-OCH_3	H
S	O		H	H	H	H
S	O	2-SO_2CH_3	H	H	H	H
S	O	2-$CH_2CH=CH_2$	H	4-$CH_2CH=CH_2$	H	H
S	O	H	3-$N(CH_3)_2$	H	H	H
S	O	H	H	4-Cl	7-S—C_6H_5	H
S	O	2-$CHCO_2$	H	H	H	H
S	O	2-Cl	H	4-SCH_2CO_2H	H	H
S	O	2-COC_3	H	H	7-OCH_3	H
S	O	H	H	4-CO—C_6H_5	7-OCH_3	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-$N(CH_3)_2$	H	H	H
S	NH	2-SCH_3	H	4-SCH_3	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-$COCH_3$	H	H	7-OCH_3	H
S	O	H	H	4-COC_6H_5	7-OCH_3	H

Y	X	R_1	R_2	R_3	R_4	T
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H
O	O	H	2-Cl	H	H	H
O	O	4-Cl	2-S-pPAA*	H	H	H
Se	O	4-Cl	H	H	H	H
Se	O	4-Cl	H	7-OMe	H	H
Se	O	4-Me	H	H	H	H
Se	O	4-Cl	2-S-pPAA*	H	H	H
N—CH_3	O	4-Cl	H	H	H	H
N—C_6H_6	O	4-Cl	H	7-OMe	H	H
N—H	O	4-Cl	2-S-pPAA*	H	H	H
S	O	4-Cl	H	H	H	H
SO	O	H	H	H	H	H
SO_2	O	H	H	H	H	H
SO_2	O	4-Cl	H	H	H	H
N—Me	O	H	H	H	H	H
N—Me	O	4-Cl	H	H	H	H
N—Me	O	4-Cl	H	7-OMe	H	H
NCN	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
NH	O	4-Cl	H	H	H	H
S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
S	O	2-t-Bu	7-t-Bu	4-F	H	H
S	O	2-t-Bu	7-t-Bu	4-Me	H	H
S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

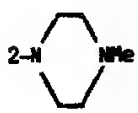
*p-PAA = para-Phenylacetic acid

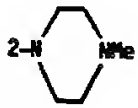
12. Tha use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula I, or a pharmaceutical composition containing such a compound, in which, in Formula I, the variables are as defined as follows, X being in the 3-position:

R_1	R_2	R_3	R_4	T
H	H	H	H	H
2-Cl	H	H	H	H
H	H	6-Cl	H	H
H	H	7-Cl	H	H
H	H	8-Cl	H	H
H	H	9-Cl	H	H
1-Cl	H	H	H	H
1-Cl	4-Cl	H	H	H
2-Cl	4-Cl	H	H	1-Cl
2-$N(Me)_2$	H	H	H	H
2-SMe	H	H	H	H
2-S-pPAA	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMa	H	H	H	H
H	H	H	7-CH_2CO_2H	H
H	H	H	8-CH_2COOH	H
H	2-SO_3H	H	H	H
2-$N(Ma)_2$	H	H	H	H
2-SMe	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMe	H	H	H	7-I
2-CH_2CO_2H	H	H	H	H

R_1	R_2	R_3	R_4	T
2-$CH(CH_3)CO_2H$	H	H	H	H
4-CH_2COOH	H	H	H	H
4-$CH(CH_3)CO_2H$	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	h
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH_2COOH	H	H	H
4-Cl	2-CH_2COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH_2COOH	H	H
4-Cl	H	7-CH_2COOH	H	H
4-Cl	H	8-CH_2COOH	H	H

R_1	R_2	R_3	R_4	T
4-Cl	2-N(Me)$_2$	H	H	H
4-Cl	1-N(Me)$_2$	H	H	H
4-Cl	2-N(Me)$_2$	7-OMe	H	H
4-Cl	2-N(Me)$_2$	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH$_2$COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO$_3$H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-(CH$_2$)$_4$—		H
4-Cl	H	7/8-(CH$_2$)$_3$—		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH$_2$	H	H	H	H
2-Me	7-N(Me)$_2$	H	H	H
7-N(Me)$_2$	H	H	H	H
1-CO$_2$H	4-OH	7-NMe$_2$	H	H

R_1	R_2	R_3	R_4	T
1-Cl	2-Cl	4-Cl	H	7-Cl
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H
H	H	H	H	4-CF_3
2-CF_3	H	H	H	4-CF_3
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H

R_1	R_2	R_3	R_4	T
	7-OMe	H	H	4-Br
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OME	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH_2	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-$NHCH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-$CH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-SO_2Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br

R_1	R_2	R_3	R_4	T
2-OMe	7-CF_3	H	H	4-Br
2-OMe	7-F	H	H	4-Br
2-OMe	7-Cl	H	H	4-Br
2-OMe	7-Br	H	H	4-Br
2-OMe	7-NMe_2	H	H	4-Br
2-OMe	7-SMe	H	H	4-Br
2-OMe	7-SO_2Me	H	H	4-Br
2-OMe	7-Ph	H	H	4-Br
1-Me	H	H	H	4-Br
2-Me	H	H	H	H
2-OEt	H	H	H	H
7-Cl	H	H	H	H
9-Cl	H	H	H	H
7-F	H	H	H	H
7-Me	H	H	H	H
7-OMe	H	H	H	H
2-Cl	H	H	H	4-Cl
1-Me	7-Me	H	H	4-Cl
1-Me	7-Me	H	H	H
2-OMe	7-OEt	H	H	H
2-NH_2	H	H	H	H
7-OH	H	H	H	H

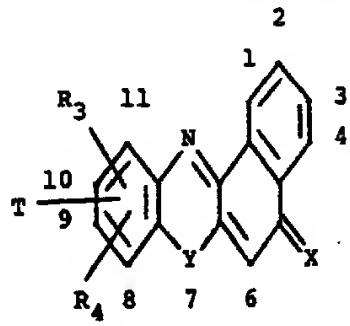
* pPAA = para-Phenylacetic Acid

and in which R is H or C_1 to C_4 alkyl.

13. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of tha Formula I, a compound that is a salt of a compound of the Formula I, or a pharmeceutical composition containing such a compound, in which, in Formula I, the variables are as defined as follows, X being in the 3-position:

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-OMe	7-OMe	H	H	H
S	O	1-OMe	7-OMe	H	H	H
S	O	2-OMe	7-OMe	H	H	1-Br
S	O	1-OMe	7-OMe	H	H	2-Br
S	O	1-OMe	7-OMe	H	H	4-Br
S	O	1-OMe	7-OMe	H	H	2-Cl
S	O	1-OMe	7-OMe	H	H	4-Cl
S	O	2-OMe	7-OMe	H	H	1-Cl
S	O	2-OMe	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OEt	H	H	1-Br
S	O	2-OEt	7-OEt	H	H	4-Br
S	O	2-OEt	7-OEt	H	H	1-Cl
S	O	2-OEt	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OMe	8-OMe	H	1-Br
S	O	2-OMe	7-OMe	8-OMe	H	4-Br
S	O	2-OMe	7-OMe	H	H	4-F
S	O	2-OMe	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OEt	H	H	4-Be
S	O	2-OMe	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OEt	H	H	4-F
S	O	2-OMe	7-OEt	H	H	4-CF_3
S	O	2-OEt	7-OMe	H	H	4-Br
S	O	2-OEt	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OMe	H	H	4-F
S	O	2-OEt	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OMe	H	H	4-Br

14. The use, for the manufacture of a medicament for inhibiting mammalian leukotriene biosynthesis or action, of a compound of the Formula I, a compound that is a salt of a compound of the Formula II:



II

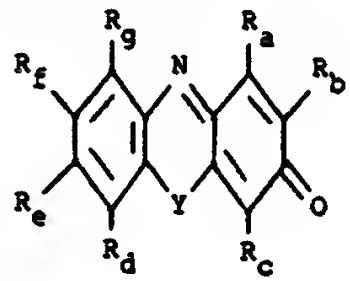
where the substituents are:

Y	X	R_3	R_4	T
O	O	H	H	H
S	O	H	H	H
SO	O	H	H	H
SO_2	O	H	H	H
SO	O	H	H	6-Cl
S	O	6-$COCH_3$	H	H
S	O	6-CH_3	H	H
SO_2	O	6-OH	H	H
SO_2	O	6-OMe	H	H
S	O	9-OMe	H	H
S	O	6-OH	H	H
S	O	6-OMe	H	H
S	O	6-NHCOMe	H	H
S	O	6-NHPh	H	H
S	O	H	H	6-Br
S	O	6-NHMe	H	H
S	O	6-NH-t-Bu	H	H
S	O	6-NH-COMe	H	9-Cl
S	O	6-NH-COMe	9-Ome	H
S	O	6-NHPh-p-Br	H	9-Cl
O	O	H	H	6-Cl
O	O	H	H	6-Br
O	O	9-OMe	H	6-Br

Y	X	R_3	R_4	T
O	O	9-OMe	6-NHPr	H
S	O	6-CF_3	H	H
S	O	6-S-n-Bu	H	H
S	O	6-OMe	H	9-Cl
S	O	9-OMe	H	6-Cl
S	O	6-OMe	9-OMe	H
S	O	6-Cl	9-Me	11-Br
S	O	6-NHPh	9-Me	11-Br
S	O	6-Me	H	H
O	NH	9-NMe_2	10-Me	H
O	NH	9-$N(Et)_2$	H	H
S	O	6-Cl	H	H

15. A use as claimed in any one of Claims 1 to 14, applied to treatment of (1) pulmonary conditions, (2) inflammation, (3) allergies, (4) pain, (5) cardiovascular conditions or (6) skin conditions.

16. The compounds of the Formula:

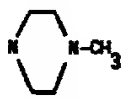
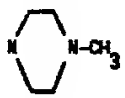
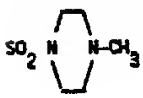


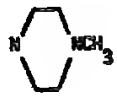
In which the substituents are:

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	SCH_3	H	H	H	H	H
S	H	H	SCF_3	H	H	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	OCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	H	H	CF_3	H	H
S	CH_3	H	Cl	H	H	H	H
S	H	CH_3	Cl	H	H	H	H

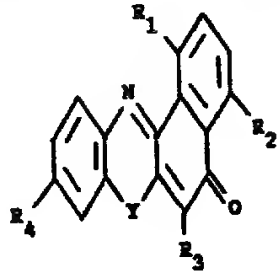
Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH_3	H	H	F	H	H
S	CH_3	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF_3	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	H	OCH_3	H	Cl	H	H
S	H	H	CF_3	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H
S	H	OCH_3	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH_3	H	H
S	H	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	H	H	H
S	H	CH_3	Br	H	H	H	H
S	CH_3	H	H	H	CH_3	H	H
S	H	CH_3	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H
SO_2	H	H	OH	H	H	H	H
SO_2	H	OMe	OH	H	OMe	H	H
SO_2	OMe	OMe	Me	H	H	H	H
SO_2	H	H	OMe	H	H	H	H
SO_2	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH_3
S	H	OCH_3	H	H	F	H	H
S	H	OCH_2H	OCH_2	H	H	H	H
S	OCH_3	OCH_3	Me	H	H	H	H
S	H	H	$COCH_3$	H	H	H	H
S	OCH_3	H	Br	H	OCH_3	H	H
S	OCH_3	Cl	Cl	H	OCH_3	H	H
S	OCH_3	H	Cl	H	OCH_2H	H	H
S	H		H	H	OCH_3	H	H
S	H		Br	H	OCH_3	H	H
SO_2	H	OCH_3	OH	H	OCH_3	H	H
SO_2	NHPr	H	NHPr	H	H	H	H
		H		H	H	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
SO_2	H	OCH_3		H	OCH_3	H	H
SO_2	H	OCH_3	Br	H	OCH_3	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH_3	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH_3	H	H
S	H	OCH_3	NH_2	H	OCH_3	H	H
S	H	OCH_3	NHPr	H	OCH_3	H	H
SO_2	H	OCH_3	NHPr	H	OCH_3	H	H
O	OCH_3	H	Cl	H	OCH_3	H	H
O	OCH_3	H	Br	H	OCH_3	H	H
O	NHPr	H	NHPr	H	H	H	H
SO_2	H	OCH_3	CN	H	OCH_3	H	H
SO_2	H	OCH_3	$NHCH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	S-N-Bu	H	OCH_3	H	H
SO_2	H	OCH_3	$CH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	SO_2CH_3	H	OCH_3	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H
S	H	CH_3	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF_3	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe_2	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO_2Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H

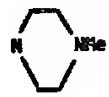
and R is H or C_2 to C_4 alkyl.

17. The compounds of the Formula:



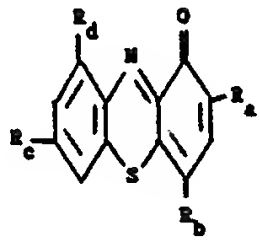
wherein the substituents are:

Y	R_1	R_2	R_3	R_4
S	H	H	S-n-CH_4H_9	H
S	OH	H	CH_3	H
S	OCH_3	H	CH_3	H
S	H	H	F	H
S	H	H	CF_3	H
S	H	H	Cl	CF_3
S	H	H	Cl	SCH_3
S	H	H	Br	Cl
S	H	H	CH_3	Br
S	H	H	F	Br
S	H	H	$COCH_3$	Cl
S	H	H	CF_3	CH_3
S	H	H	SC_4H_9	CH_3
S	H	H	CF_3	Cl
S	H	H	Cl	CH_2COOR
S	H	H	Cl	$CH(Me)CO_2R$
S	H	H	Cl	$COCH_3$
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF_3
S	H	H	H	CH_3
S	H	H	H	CH_2OH
S	H	H	H	OCH_3
S	H	H	H	SCH_3

Y	R_1	R_2	R_3	R_4
S	H	H	H	COOR
S	H	H	H	CH_2CO_2R
S	H	H	H	$CH(Me)CO_2R$
SO_2	H	H	NHPr	H
SO_2	H	H		H
SO_2	H	H	NH_2	H
SO_2	H	H	NHPr	OCH_3
S	-1,4-dihydro-		H	H
S	H	H	NHPr	OCH_3
O	H	H	Cl	H
O	H	H	Br	H
O	H	H	Br	OCH_3
O	H	H	NHPr	OCH_3

and wherein R is H or C_1 to C_4 alkyl.

18. The compounds of the formula:



III

where the substituents are:

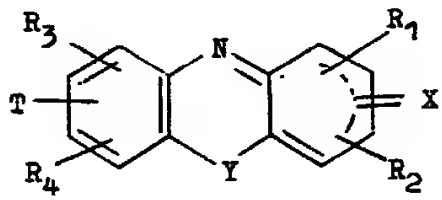
R_a	R_b	R_c	R_d
t-Bu	t-Bu	H	H
t-Bu	t-Bu	F	H
t-Bu	t-Bu	Me	H
t-Bu	t-Bu	SMe	H
t-Bu	t-Bu	H	OMe

19. The compounds 2-S-glutathionyl-3H-phenothiazin-3-one and 4-chloro-2-S-glutathionyl-phenothiazin-3-one.

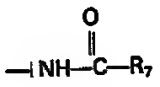
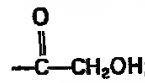
20. The use claimed in Claim 1 of the manufacture of a medicament that additionelly contains a second active ingredent that is a non-steroidal antiinflammatory agent; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist, an antihistaminic agent; a prostaglandin antagonist; or a thromboxane antagonist, in which the weight ratio of the Formula I compound to the second active ingredient ranges from 10:1 to 1:10.

Patentansprüche

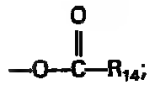
1. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung entheltenden pharmazeutischen Zusammensetzung:

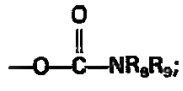


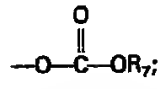
I

worin
X in der 1- oder 3-Stellung ist und O, S oder NR ist;
R H, verzweigtes oder lineares C_{1-6}-Alkyl, CN oder Phenyl ist;
Y O, Se, S, SO, SO_2 oder NR ist; und die gestrichelte Linie eine Doppelbindung zwischen der 1- und 2- oder 2- und 3-Stellung darstellt;
jedes von R_1, R_2, R_3 und R_4 unabhängig von den anderen
(1) Wasserstoff,
(2) $_{1-6}$-Alkyl,
(3) $_{2-6}$-Alkenyl,
(4) $—(CH_2)_nM$ ist,
worin n 0 oder eine ganze Zahl von 1 bis 6 ist und M
(a) OR_6,
(b) Halogen,
(c) CF_3,
(d) SR_6, worin R_6 H; C_{1-6}-Alkyl; Benzyl; Phenyl oder substituiertes Phenyl, worin die Substituenten C_{1-3}-Alkyl, Halogen, CN, CF_3, $COOR_6$, CN_2COOR_6, $(CH_2)_nNR_6R_9$ worin n 0, 1 oder 2 ist, C_{1-3}-Alkoxy, OH oder C_{1-6}-Halogenelkyl; sind; $—(CH_2)_mCOOR_6$, worin m 0 oder eine ganze Zahl von 1 bis 6 ist und R_6 H, Phenyl oder C_{1-6}-Alkyl; CN, Formyl, CF_3 oder $CH_2—R_{12}$, worin R_{12} C_{1-6}-Alkyl, Phenyl oder Dimethylamino ist; ist,
(e) Phenyl oder substituiertes Phenyl, wie oben für R_5 definiert;
(f) $COOR_6$;
(g) 
worin R_{15} H, $(CH_2)_n$ $COOR_6$, worin n 0 oder eine ganze Zahl von 1 bis 4 ist, C_{1-6}-Alkyl, CF_3, Phenyl oder substituiertes Phenyl, wie oben für R_5 definiert;
(h) Tetrazol;
(i) 
worin R_7 C_{1-6}-Alkyl, Benzyl oder Phenyl ist;
(j) $—NR_8R_9$ worin R_8 und R_9 unabhängig aus H, Phenyl oder substituiertem Phenyl, wie oben für R_5 definiert, oder C_{1-4}-Alkyl, C_{1-4}-Alkylaminoalkyl ausgewählt sind, oder über das N unter Bildung eines 4-Methylpiperazinylrestes verbunden sein können;
(k) $—NHSO_2R_{10}$, worin R_{10} OH, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, Phenyl oder CF_2 ist;
(l) 
(m) $—SOR_{11}$, worin R_{11} C_{1-6}-Alkyl, Phenyl oder substituiertes Phenyl, wie oben für R_5 definiert, $(CH_2)_mCOOR_6$, worin m 1 bis 6 ist, CN, Formyl oder CF_3 ist;
(n) $—CONR_8R_9$;
(o) $—SO_2NR_8R_9$;
(p) $—SO_2R_{13}$, worin R_{13} OH, H, C_{1-6}-Alkyl, Phenyl oder substituiertes Phenyl, wie oben für R_5 definiert, $(CH_2)_mCOOR_6$, worin m 1 bis 6 ist, CN oder CF_3 ist;

(q) NO_2;

(r)  ;

(s)  ;

(t)  ;

(u) —CN; oder

(v) $NR_{15}R_{16}$ worin R_{15} und R_{16} so sind, daß $HNR_{15}R_{16}$ eine essentielle Aminosäure darstellt; oder jeweils zwei von R_1, R_2, R_3 und R_4 unter Bildung eines vierten gesättigten oder ungesättigten C_5—C_8-Rings zusammengenommen werden; und T H, Halogen oder CF_3 ist.

2. Verwendung, wie in Anspruch 1 beansprucht, worin in Formel I X in der 1-Stellung ist.

3. Verwendung, wie in Anspruch 2 beansprucht, worin X O oder NR ist.

4. Verwendung, wie in Anspruch 3 beansprucht, worin in Formel I Y S, SO, SO_2, NR oder O ist und in der Struktureinheit $(CH_2)_nM$ n 0 oder 1 ist.

5. Verwendung, wie in Anspruch 4 beansprucht, worin in Formel I X O ist und Y S ist.

6. Verwendung, wie in Anspruch 1 beansprucht, worin in Formel I X in der 3-Stellung ist.

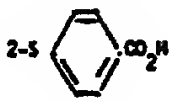
7. Verwendung, wie in Anspruch 6 beansprucht, worin X O oder NR ist.

8. Verwendung, wie in Anspruch 7 beensprucht, worin in Formel I Y S, SO, SO_2, NR oder O ist und in der Struktureinheit $(CH_2)_nM$ n 0 oder 1 ist.

9. Verwendung, wie in Anspruch 8 beansprucht, worin Y S oder O ist.

10. Verwendung, wie in Anspruch 9 beansprucht, worin X O ist und Y S ist.

11. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung, worin in der Formel I die Variablen wie nachstehend definiert sind und X in der 1-Stellung ist.

Y	X	R_1	R_2	R_3	R_4	T
O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
O	O	2-t-Bu	H	4-Me	H	H
S	S	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO oder SO_2	O	2-Cl	H	H	H	H
"	O	2-SCF_3	H	H	H	H
"	O	2-5 	H	H	H	H
S	O	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO oder SO_2	O	2-CN	H	H	H	H
"	O	H	3-CO_2Et	H	H	H
"	O	H	3-Cl	H	H	H
"	O	H	H	4-Cl	H	H
"	O	H	H	4-SO_2CH_3	H	H

Y	X	R_1	R_2	R_3	R_4	T
SO_2	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N—CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	$7\text{-}SO_2CH_3$	H
S	O	2-Cl	H	$4\text{-}SO_2CH_3$	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	$2\text{-}CF_3$	H	H	H	H
S	O	$2\text{-}SCF_3$	H	H	H	H
S	O	$2\text{-}SO_2CF_3$	H	H	H	H
S	O	H	3-Cl	H	H	H
S	O	H	$3\text{-}CO_2Et$	H	H	H
S	O	H	$3\text{-}CO_2H$	H	H	H
S	O	H	3-CN	H	H	H
S	O	H	$3\text{-}SCF_3$	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	$4\text{-}SCF_3$	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	$8\text{-}CO_2Et$	H
S	O	2-Cl	H	H	$8\text{-}CO_2H$	H
S	O	2-Cl	H	H	$8\text{-}CF_3$	H
S	O	2-Cl	H	H	$7\text{-}SO_2CH_3$	H
S	O	H	$3\text{-}CONMe_2$	H	H	H
S	O	2-Cl	H	H	$7\text{-}OCH_3$	H

Y	X	R_1	R_2	R_3	R_4	T
S	O		H	H	H	H
S	O	2-SO_2CH_3	H	H	H	H
S	O	2-$CH_2CH{=}CH_2$	H	4-$CH_2CH{=}CH_2$	H	H
S	O	H	3-$N(CH_3)_2$	H	H	H
S	O	H	H	4-Cl	7-S—C_6H_6	H
S	O	2-$CHCO_2$	H	H	H	H
S	O	2-Cl	H	4-SCH_2CO_2H	H	H
S	O	2-COC_3	H	H	7-OCH_3	H
S	O	H	H	4-CO—C_6H_6	7-OCH_3	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-$N(CH_3)_2$	H	H	H
S	NH	2-SCH_3	H	4-SCH_3	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-$COCH_3$	H	H	7-OCH_3	H
S	O	H	H	4-COC_6H_5	7-OCH_3	H
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
O	O	H	2-Cl	H	H	H
O	O	4-Cl	2-S-pPAA*	H	H	H
Se	O	4-Cl	H	H	H	H
Se	O	4-Cl	H	7-OMe	H	H
Se	O	4-Me	H	H	H	H
Se	O	4-Cl	2-S-pPAA*	H	H	H
N—CH_3	O	4-Cl	H	H	H	H
N—C_6H_6	O	4-Cl	H	7-OMe	H	H
N—H	O	4-Cl	2-S-pPAA*	H	H	H
S	O	4-Cl	H	H	H	H
SO	O	H	H	H	H	H
SO_2	O	H	H	H	H	H
SO_2	O	4-Cl	H	H	H	H
N—Me	O	H	H	H	H	H
N—Me	O	4-Cl	H	H	H	H
N—Me	O	4-Cl	H	7-OMe	H	H
NCN	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H
S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
S	O	2-t-Bu	7-t-Bu	4-F	H	H
S	O	2-t-Bu	7-t-Bu	4-Me	H	H
S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

*pPAA = Paraphenylessigsäure

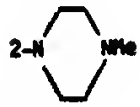
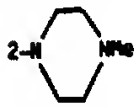
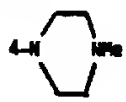
12. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmezeutischen Zusammensetzung, worin in Formel I die Variablen wie nachstehend definiert sind und X in der 3-Stellung ist.

R_1	R_2	R_3	R_4	T
H	H	H	H	H
2-Cl	H	H	H	H
H	H	6-Cl	H	H
H	H	7-Cl	H	H

R_1	R_2	R_3	R_4	T
H	H	8-Cl	H	H
H	H	9-Cl	H	H
1-Cl	H	H	H	H
1-Cl	4-Cl	H	H	H
2-Cl	4-Cl	H	H	1-Cl
2-$N(Me)_2$	H	H	H	H
2-SMe	H	H	H	H
2-S-pPAA	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMe	H	H	H	H
H	H	H	7-CH_2CO_2H	H
H	H	H	8-CH_2COOH	H
H	2-SO_3H	H	H	H
2-$N(Me)_2$	H	H	H	H
2-SMe	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMe	H	H	H	7-I
2-CH_2CO_2H	H	H	H	H
2-$CH(CH_3)CO_2H$	H	H	H	H
4-CH_2COOH	H	H	H	H
4-$CH(CH_3)CO_2H$	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H

R_1	R_2	R_3	R_4	T
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	h
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH_2COOH	H	H	H
4-Cl	2-CH_2COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH_2COOH	H	H
4-Cl	H	7-CH_2COOH	H	H
4-Cl	H	8-CH_2COOH	H	H
4-Cl	2-$N(Me)_2$	H	H	H
4-Cl	1-$N(Me)_2$	H	H	H
4-Cl	2-$N(Me)_2$	7-OMe	H	H
4-Cl	2-$N(Me)_2$	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH_2COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO_3H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H

R_1	R_2	R_3	R_4	T
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-$(CH_2)_4$—		H
4-Cl	H	7/8-$(CH_2)_3$—		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH_2	H	H	H	H
2-Me	7-$N(Me)_2$	H	H	H
7-$N(Me)_2$	H	H	H	H
1-CO_2H	4-OH	7-NMe_2	H	H
1-Cl	2-Cl	4-Cl	H	7-Cl
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H

R_1	R_2	R_3	R_4	T
H	H	H	H	4-CF_3
2-CF_3	H	H	H	4-CF_3
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H
	7-OMe	H	H	4-Br
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OME	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H

R_1	R_2	R_3	R_4	T
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH_2	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-$NHCH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-$CH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-SO_2Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br
2-OMe	7-CF_3	H	H	4-Br
2-OMe	7-F	H	H	4-Br
2-OMe	7-Cl	H	H	4-Br
2-OMe	7-Br	H	H	4-Br
2-OMe	7-NMe_2	H	H	4-Br
2-OMe	7-SMe	H	H	4-Br
2-OMe	7-SO_2Me	H	H	4-Br
2-OMe	7-Ph	H	H	4-Br
1-Me	H	H	H	4-Br
2-Me	H	H	H	H
2-OEt	H	H	H	H
7-Cl	H	H	H	H
9-Cl	H	H	H	H
7-F	H	H	H	H
7-Me	H	H	H	H

R_1	R_2	R_3	R_4	T
7-OMe	H	H	H	H
2-Cl	H	H	H	4-Cl
1-Me	7-Me	H	H	4-Cl
1-Me	7-Me	H	H	H
2-OMe	7-OEt	H	H	H
2-NH_2	H	H	H	H
7-OH	H	H	H	H

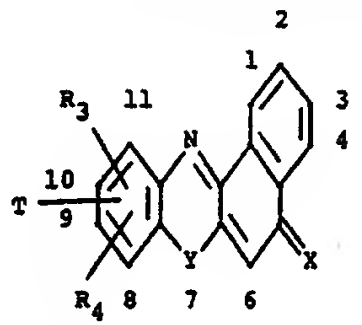
pPAA = Paraphenylessigsäure und worin R H oder C_1—C_4-Alkyl ist.

13. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel I ist, oder einer eine solche Verbindung enthaltenden pharmazeutischen Zusammensetzung, worin in Formel I die Variablen wie nachstehend definiert sind und X in der 3-Stellung ist:

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-OMe	7-OMe	H	H	H
S	O	1-OMe	7-OMe	H	H	H
S	O	2-OMe	7-OMe	H	H	1-Br
S	O	1-OMe	7-OMe	H	H	2-Br
S	O	1-OMe	7-OMe	H	H	4-Br
S	O	1-OMe	7-OMe	H	H	2-Cl
S	O	1-OMe	7-OMe	H	H	4-Cl
S	O	2-OMe	7-OMe	H	H	1-Cl
S	O	2-OMe	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OEt	H	H	1-Br
S	O	2-OEt	7-OEt	H	H	4-Br
S	O	2-OEt	7-OEt	H	H	1-Cl
S	O	2-OEt	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OMe	8-OMe	H	1-Br
S	O	2-OMe	7-OMe	8-OMe	H	4-Br
S	O	2-OMe	7-OMe	H	H	4-F
S	O	2-OMe	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OEt	H	H	4-Be
S	O	2-OMe	7-OEt	H	H	4-Cl

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-OMe	7-OEt	H	H	4-F
S	O	2-OMe	7-OEt	H	H	4-CF_3
S	O	2-OEt	7-OMe	H	H	4-Br
S	O	2-OEt	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OMe	H	H	4-F
S	O	2-OEt	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OMe	H	H	4-Br

14. Verwendung, zur Herstellung eines Medikaments zur Inhibierung der Leukotrienbiosynthese oder -wirkung in Säugetieren, einer Verbindung der Formel I, einer Verbindung, die ein Salz einer Verbindung der Formel II ist:



II

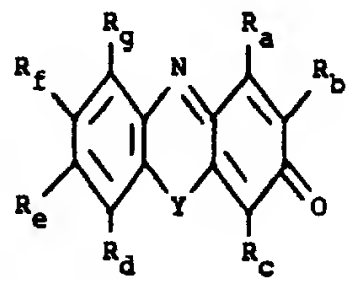
worin die Substituenten wie folgt sind:

Y	X	R_3	R_4	T
O	O	H	H	H
S	O	H	H	H
SO	O	H	H	H
SO_2	O	H	H	H
SO	O	H	H	6-Cl
S	O	6-$COCH_3$	H	H
S	O	6-CH_3	H	H
SO_2	O	6-OH	H	H
SO_2	O	6-OMe	H	H
S	O	9-OMe	H	H
S	O	6-OH	H	H
S	O	6-OMe	H	H
S	O	6-NHCOMe	H	H
S	O	6-NHPh	H	H

Y	X	R_3	R_4	T
S	O	H	H	6-Br
S	O	6-NHMe	H	H
S	O	6-NH-t-Bu	H	H
S	O	6-NH-COMe	H	9-Cl
S	O	6-NH-COMe	9-Ome	H
S	O	6-NHPh-p-Br	H	9-Cl
O	O	H	H	6-Cl
O	O	H	H	6-Br
O	O	9-OMe	H	6-Br
O	O	9-OMe	6-NHPr	H
S	O	6-CF_3	H	H
S	O	6-S-n-Bu	H	H
S	O	6-OMe	H	9-Cl
S	O	9-OMe	H	6-Cl
S	O	6-OMe	9-OMe	H
S	O	6-Cl	9-Me	11-Br
S	O	6-NHPh	9-Me	11-Br
S	O	6-Me	H	H
O	NH	9-NMe_2	10-Me	H
O	NH	9-$N(Et)_2$	H	H
S	O	6-Cl	H	H

15. Verwendung, wie in einem der Ansprüche 1 bis 14 beansprucht, angewandt auf die Behandlung von (1) Lungenzuständen, (2) Entzündungen, (3) Allergien, (4) Schmerz, (5) cardiovaskuläre Zustände oder (6) Hautzustände.

16. Verbindungen der Formel

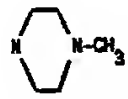
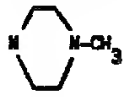
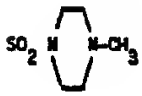
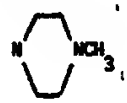


worin die Substituenten wie folgt sind:

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	SCH_3	H	H	H	H	H
S	H	H	SCF_3	H	H	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	OCH_3	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	H	H	CF_3	H	H
S	CH_3	H	Cl	H	H	H	H
S	H	CH_3	Cl	H	H	H	H
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH_3	H	H	F	H	H
S	CH_3	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF_3	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	H	OCH_3	H	Cl	H	H
S	H	H	CF_3	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H

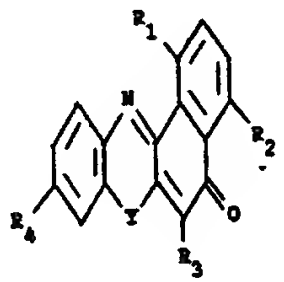
Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	OCH_3	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH_3	H	H
S	H	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	H	H	H
S	H	CH_3	Br	H	H	H	H
S	CH_3	H	H	H	CH_3	H	H
S	H	CH_3	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H
SO_2	H	H	OH	H	H	H	H
SO_2	H	OMe	OH	H	OMe	H	H
SO_2	OMe	OMe	Me	H	H	H	H
SO_2	H	H	OMe	H	H	H	H
SO_2	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH_3
S	H	OCH_2	H	H	F	H	H
S	H	OCH_3H	OCH_3	H	H	H	H
S	OCH_3	OCH_3	Me	H	H	H	H
S	H	H	$COCH_3$	H	H	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	OCH_3	H	Br	H	OCH_3	H	H
S	OCH_3	Cl	Cl	H	OCH_3	H	H
S	OCH_3	H	Cl	H	OCH_3H	H	H
S	H		H	H	OCH_3	H	H
S	H		Br	H	OCH_3	H	H
SO_2	H	OCH_3	OH	H	OCH_3	H	H
SO_2	NHPr	H	NHPr	H	H	H	H
		H		H	H	H	H
SO_2	H	OCH_3		H	OCH_3	H	H
SO_2	H	OCH_3	Br	H	OCH_3	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH_3	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH_3	H	H
S	H	OCH_3	NH_2	H	OCH_3	H	H
S	H	OCH_3	NHPr	H	OCH_3	H	H
SO_2	H	OCH_3	NHPr	H	OCH_3	H	H
O	OCH_3	H	Cl	H	OCH_3	H	H
O	OCH_3	H	Br	H	OCH_3	H	H
O	NHPr	H	NHPr	H	H	H	H
SO_2	H	OCH_3	CN	H	OCH_3	H	H
SO_2	H	OCH_3	$NHCH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	S-N-Bu	H	OCH_3	H	H
SO_2	H	OCH_3	$CH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	SO_2CH_3	H	OCH_3	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	CH_3	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF_3	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe_2	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO_2Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H

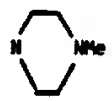
und R H oder C_2—C_4-Alkyl ist.

17. Verbindungen der Formel



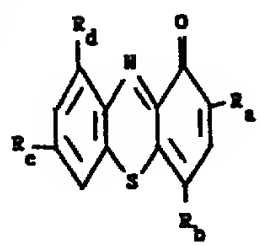
worin die Substituenten wie folgt sind:

Y	R_1	R_2	R_3	R_4
S	H	H	S-n-CH_4H_9	H
S	OH	H	CH_3	H
S	OCH_3	H	CH_3	H
S	H	H	F	H
S	H	H	CF_3	H
S	H	H	Cl	CF_3
S	H	H	Cl	SCH_3
S	H	H	Br	Cl
S	H	H	CH_3	Br
S	H	H	F	Br
S	H	H	$COCH_3$	Cl
S	H	H	CF_3	CH_3
S	H	H	SC_4H_9	CH_3

Y	R_1	R_2	R_3	R_4
S	H	H	CF_3	Cl
S	H	H	Cl	CH_2COOR
S	H	H	Cl	$CH(Me)CO_2R$
S	H	H	Cl	$COCH_3$
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF_3
S	H	H	H	CH_3
S	H	H	H	CH_2OH
S	H	H	H	OCH_3
S	H	H	H	SCH_3
S	H	H	H	COOR
S	H	H	H	CH_2CO_2R
S	H	H	H	$CH(Me)CO_2R$
SO_2	H	H	NHPr	H
SO_2	H	H		H
SO_2	H	H	NH_2	H
SO_2	H	H	NHPr	OCH_3
S	-1,4-dihydro-		H	H
S	H	H	NHPr	OCH_3
O	H	H	Cl	H
O	H	H	Br	H
O	H	H	Br	OCH_3
O	H	H	NHPr	OCH_3

und worin R H oder C_1—C_4-Alkyl ist.

18. Verbindungen der Formel



III

worin die Substituenten wie folgt sind:

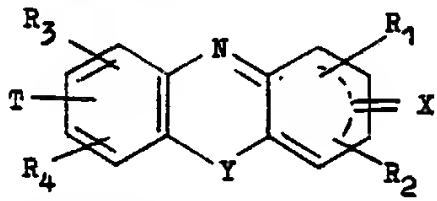
R_a	R_b	R_c	R_d
t-Bu	t-Bu	H	H
t-Bu	t-Bu	F	H
t-Bu	t-Bu	Me	H
t-Bu	t-Bu	SMe	H
t-Bu	t-Bu	H	OMe

19. Die Verbindung 2-S-Glutathionyl-3H-phenothiazin-3-on und 4-Chlor-2-S-glutathionylphenothiezin-3-on.

20. Die in Anspruch 1 beansprucht Verwendung zur Herstellung eines Medikaments, die zusätzlich einen zweiten aktiven Bestandteil enthält, der ein nicht-steroides entzündungshemmendes Mittel ist; ein peripheres Analgetikum, ein Cyclooxygenaseinhibitor; ein Leukotrienentagonist; ein Antihistaminikum; ein Prostaglendinantagonist; oder ein Thromboxanentagonist, wobei das Gewichtsverhältnis der Verbindung der Formel I zum zweiten aktiven Bsestandteil im Bereich von 10:1 bis 1:10 liegt.

Revendications

1. L'utillsation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'ection daa leucotriènea chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenent un tel composé:



I

dens lequelle

X est dane le position 1 ou 3 et est O, S ou NR;

R est H, un elkyle remifié ou linéeire en C_{1-6}, CN ou un phényle;

Y est O, Se, S, SO, SO_2 ou NR; et le pointillé représente une doubla liaison entre las positions 1 at 2 ou 2 et 3;

checun de R_1, R_2, R_3 et R_4 indépendamment des autres est:

(1) un hydrogène,

(2) un alkyla an C_{1-6},

(3) un alcényle en C_{2-6},

(4) $—(CH_2)_nM$

où n est 0 ou un entier de 1 à 6 et M est

(a) OR_5,

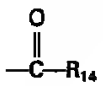
(b) un halogène,

(c) CF_3,

(d) SR_5, où R_5 est H; un alkyle en $C_1—C_6$; un benzyle; un phényle ou un phényle substitué dont les substituants sont un alkyle en C_{1-3}, un halogène, CN, CF_3, $COOR_6$, CH_2COOR_6, $(CH_2)_nNR_8R_9$ où n est 0, 1 ou 2, un alcoxy en C_{1-3}, OH ou un halogénoalkylene en C_{1-6}; $—(CH_2)_mCOOR_6$, où m est 0 ou un entier de 1 à 6 et R_6 est H, un phényle ou un alkyle en C_{1-6}; CN, un formyle, CF_3 ou $CH_2—R_{12}$, où R_{12} est un alkyle en C_{1-5}, un phényle ou un diméthylamino;

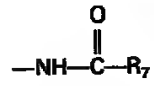
(e) un phényle ou un phényle substitué comme défini ci-dessus pour R_5;

(f) $COOR_6$;

(g) 

où R_{14} est H, $(CH_2)_nCOOR_6$ où n est 0 ou un entier de 1 à 4, un alkyle en C_{1-6}, CF_3, un phényle ou un phényle substitué comme défini ci-dessus pour R_5;

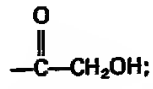
(h) un tétrazole;

(i) 

où R_7 est un alkyle en C_{1-6}, un benzyle ou un phényle;

(j) $—NR_8R_9$ où R_8 et R_9 sont indépendamment choisis parmi H, un phénylе ou un phénylе substitué comme défini ci-dessus pour R_6 ou un alkyle en C_{1-4}, un alkyl(C_{1-4})aminoalkyle ou peuvent être unis par N pour former un radicel 4-méthylpipérazinyle;

(k) $—NHSO_2R_{10}$ où R_{10} est OH, un alkyle en C_{1-6}, un alcoxy en C_{1-6}, un phénylе ou CF_3;

(l) 

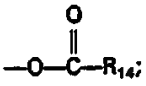
(m) $—SOR_{11}$ où R_{11} est un alkyle en C_{1-6}, un phénylе ou un phénylе substitué comme défini ci-dessus pour R^6, $(CH_2)_mCOOR_6$ où m est 1 à 6, CN, un formyle ou CF_3;

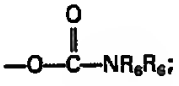
(n) $—CONR_8R_9$;

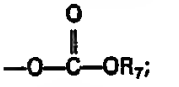
(o) $—SO_2NR_8R_9$;

(p) $—SO_2R_{13}$ où R_{13} est OH, H, un alkyle en C_{1-6}, un phénylе ou un phénylе substitué comme défini ci-dessus pour R_5, $(CH_2)_mCOOR_6$ où m est 1 à 6, CN ou CF_3;

(q) NO_2;

(r) 

(s) 

(t) 

(u) —CN; ou

(v) $NR_{15}R_{16}$ où R_{15} et R_{16} sont chacun tels que $HNR_{15}R_{16}$ soit un amino-acide essentiel;

ou deux quelconques de R_1, R_2, R_3 et R_4 sont unis pour former un quatrième cycle saturé ou insaturé en C_{5-6}; et

T est H, un halogène ou CF_3.

2. L'utilisation selon la revendication 1, dans laquelle, dans la formule I, X est en position 1.

3. L'utilisation selon la revendication 2, dans laquelle X est O ou NR.

4. L'utilisation selon la revendication 3, dans laquelle, dans la formule I, Y est S, SO, SO_2, NR ou O et dans l'unité structurale $(CH_2)_nM$, n est 0 ou 1.

5. L'utilisation selon la revendication 4, dans laquelle, dans la formule I, X est O et Y est S.

6. L'utilisation selon la revendication 1, dans laquelle, dans la formule I, X est en la position 3.

7. L'utilisation selon la revendication 6, dans laquelle X est O ou NR.

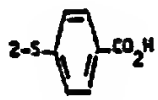
8. L'utilisation selon la revendication 7, dans laquelle, dans la formule I, Y est S, SO, SO_2, NR ou O et dans l'unité structurale $(CH_2)_nM$, n est 0 ou 1.

9. L'utilisation selon la revendication 8, dans laquelle Y est S ou O.

10. L'utilisation selon la revendication 9, dans laquelle X est O et Y est S.

11. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'ection des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans la formule I, les variables sont comme défini ci-après, X étant en position 1:

Y	X	R_1	R_2	R_3	R_4	T
O	O	2-t-Bu	8-t-Bu	4-t-Bu	6-t-Bu	H
O	O	2-t-Bu	H	4-Me	H	H
S	S	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO ou SO_2	O	2-Cl	H	H	H	H
"	O	2-SCF_3	H	H	H	
"	O		H	H	H	H
S	O	2-t-Bu	4-t-Bu	H	H	H
N—CH_3, S, O, Se, SO ou SO_2	O	2-CN	H	H	H	H
"	O	H	3-CO_2Et	H	H	H
"	O	H	3-Cl	H	H	H
"	O	H	H	4-Cl	H	H
"	O	H	H	4-SO_2CH_3	H	H
"	O	2-Cl	H	4-Cl	H	H
"	NH	2-Cl	H	4-Cl	H	H
"	NH	H	H	H	H	H
N—CN	O	2-Cl	H	4-Cl	H	H
S	O	H	H	H	H	H
S	O	2-Cl	3-Cl	4-Cl	7-Cl	9-Cl
S	O	2-Br	3-Br	4-Br	7-Br	9-Br
S	O	H	H	H	7-SO_2CH_3	H
S	O	2-Cl	H	4-SO_2CH_3	H	H
S	O	2-F	H	4-Cl	H	H
S	O	2-Br	H	H	H	H
S	O	2-CF_3	H	H	H	H
S	O	2-SCF_2	H	H	H	H
S	O	2-SO_2CF_3	H	H	H	H
S	O	H	3-Cl	H	H	H
S	O	H	3-CO_2Et	H	H	H
S	O	H	3-CO_2H	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
S	O	H	3-CN	H	H	H
S	O	H	3-SCF_3	H	H	H
S	O	H	H	4-Cl	H	H
S	O	H	H	4-SCF_3	H	H
S	O	H	H	4-Cl	H	H
S	O	2-Br	H	4-Br	H	H
S	O	2-Cl	H	H	8-CN	H
S	O	2-Cl	H	H	8-CO_2Et	H
S	O	2-Cl	H	H	8-CO_2H	H
S	O	2-Cl	H	H	8-CF_3	H
S	O	2-Cl	H	H	7-SO_2CH_3	H
S	O	H	3-$CONMe_2$	H	H	H
S	O	2-Cl	H	H	7-OCH_3	H
S	O		H	H	H	H
S	O	2-SO_2CH_3	H	H	H	H
S	O	2-$CH_2CH{=}CH_2$	H	4-$CH_2CH{=}CH_2$	H	H
S	O	H	3-$N(CH_3)_2$	H	H	H
S	O	H	H	4-Cl	7-S—C_6H_5	H
S	O	2-$CHCO_2$	H	H	H	H
S	O	2-Cl	H	4-SCH_2CO_2H	H	H
S	O	2-COC_3	H	H	7-OCH_3	H
S	O	H	H	4-CO—C_6H_5	7-OCH_3	H
S	NH	2-Cl	H	4-Cl	H	H
S	NH	H	3-$N(CH_3)_2$	H	H	H
S	NH	2-SCH_3	H	4-SCH_3	H	H
S	O	H	H	H	H	H
S	NH	H	H	H	H	H
S	O	2-$COCH_3$	H	H	7-OCH_3	H
S	O	H	H	4-COC_6H_5	7-OCH_3	H
S	NH.HCl	H	H	H	H	H
S	O	H	H	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
O	O	H	H	H	H	H
O	NH	H	H	H	H	H
O	S	H	H	H	H	H
O	NH.HCl	H	H	H	H	H
Se	O	H	H	H	H	H
Se	NH	H	H	H	H	H
Se	S	H	H	H	H	H
NH	NH.HCl	H	H	H	H	H
NH	S	H	H	H	H	H
O	O	4-Cl	H	H	H	H
O	O	4-Cl	H	7-OMe	H	H
O	O	4-Me	H	H	H	H
O	O	H	2-Cl	H	H	H
O	O	4-Cl	2-S-pPAA*	H	H	H
Se	O	4-Cl	H	H	H	H
Se	O	4-Cl	H	7-OMe	H	H
Se	O	4-Me	H	H	H	H
Se	O	4-Cl	2-S-pPAA*	H	H	H
N—CH_3	O	4-Cl	H	H	H	H
N—C_6H_6	O	4-Cl	H	7-OMe	H	H
N—H	O	4-Cl	2-S-pPAA*	H	H	H
S	O	4-Cl	H	H	H	H
SO	O	H	H	H	H	H
SO_2	O	H	H	H	H	H
SO_2	O	4-Cl	H	H	H	H
N—Me	O	H	H	H	H	H
N—Me	O	4-Cl	H	H	H	H
N—Me	O	4-Cl	H	7-OMe	H	H
NCN	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H
NH	O	4-Cl	H	H	H	H

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-t-Bu	9-t-Bu	4-OMe	H	H
S	O	2-t-Bu	7-t-Bu	4-F	H	H
S	O	2-t-Bu	7-t-Bu	4-Me	H	H
S	O	2-t-Bu	7-t-Bu	4-SMe	H	H

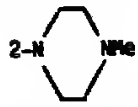
*pPAA = acide paraphénylacétique.

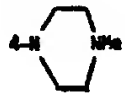
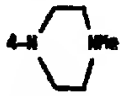
12. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans la formule I, les variables sont comme défini ci-après, X étant en position 3:

R_1	R_2	R_3	R_4	T
H	H	H	H	H
2-Cl	H	H	H	H
H	H	6-Cl	H	H
H	H	7-Cl	H	H
H	H	8-Cl	H	H
H	H	9-Cl	H	H
1-Cl	H	H	H	H
1-Cl	4-Cl	H	H	H
2-Cl	4-Cl	H	H	1-Cl
2-$N(Me)_2$	H	H	H	H
2-SMe	H	H	H	H
2-S-pPAA	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMe	H	H	H	H
H	H	H	7-CH_2CO_2H	H
H	H	H	8-CH_2COOH	H
H	2-SO_3H	H	H	H
2-$N(Me)_2$	H	H	H	H
2-SMe	H	H	H	H
2-$C(O)CH_3$	H	H	H	H
2-OMe	H	H	H	7-I
2-CH_2CO_2H	H	H	H	H
2-$CH(CH_3)CO_2H$	H	H	H	H

R_1	R_2	R_3	R_4	T
4-CH_2COOH	H	H	H	H
4-$CH(CH_3)CO_2H$	H	H	H	H
H	H	7-OH	6-propyl	H
4-Cl	H	H	H	H
4-F	H	H	H	H
4-F	H	7-Cl	H	H
4-Et	H	H	H	H
4-Et	H	7-OMe	H	H
4-Et	H	7-Cl	H	H
4-Cl	H	7-OMe	H	H
4-OMe	H	7-Cl	H	H
4-Cl	H	6-Cl	H	H
4-Cl	H	8-Cl	H	H
4-Cl	H	9-Cl	H	H
4-Cl	H	6-OMe	H	H
4-Cl	H	8-OMe	H	H
4-Cl	H	9-Et	H	h
4-Cl	H	6-Et	H	H
4-Cl	H	7-Et	H	H
4-Cl	H	8-Et	H	H
4-Cl	1-Et	H	H	H
4-Cl	2-Et	H	H	H
4-Cl	1-CH_2COOH	H	H	H
4-Cl	2-CH_2COOH	H	H	H
4-OH	2-OMe	7-OMe	H	H
4-OH	H	H	H	H
4-Me	1-OMe	2-OMe	H	H
4-Cl	H	6-CH_2COOH	H	H
4-Cl	H	7-CH_2COOH	H	H
4-Cl	H	8-CH_2COOH	H	H
4-Cl	2-$N(Me)_2$	H	H	H

R_1	R_2	R_3	R_4	T
4-Cl	1-$N(Me)_2$	H	H	H
4-Cl	2-$N(Me)_2$	7-OMe	H	H
4-Cl	2-$N(Me)_2$	7-Cl	H	H
4-Cl	2-SMe	H	H	H
4-Cl	2-SCH_2COOH	H	H	H
4-Cl	2-S-pPAA	H	H	H
4-Cl	1-S-pPAA	H	H	H
4-Cl	2-S-pPAA	7-OMe	H	H
4-Cl	2-SO_3H	H	H	H
4-Cl	2-OMe	H	H	H
4-Cl	2-OMe	7-Cl	H	H
4-Cl	H	7F	H	H
4-OMe	H	7-OMe	H	H
4-OMe	H	7-Me	H	H
4-OMe	2-SMe	H	H	H
4-SMe	H	H	H	H
4-Br	H	H	H	H
4-I	H	H	H	H
4-Br	H	7-OMe	H	H
4-I	H	7-OMe	H	H
4-Br	2-Me	H	H	H
4-I	2-Me	H	H	H
4-Cl	H	7/8-$(CH_2)_4$—		H
4-Cl	H	7/8-$(CH_2)_3$—		H
4-Br	2-OMe	7-OMe	H	H
7-F	H	H	H	H
7-NH_2	H	H	H	H
2-Me	7-$N(Me)_2$	H	H	H
7-$N(Me)_2$	H	H	H	H
1-CO_2H	4-OH	7-NMe_2	H	H
1-Cl	2-Cl	4-Cl	H	7-Cl

R_1	R_2	R_3	R_4	T
1-Me	7-Me	H	H	4-Cl
2-Me	7-Me	H	H	4-Cl
2-Me	H	H	H	4-Cl
7-Me	H	H	H	4-Cl
9-OMe	H	H	H	H
2-OMe	H	H	H	7-F
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	7-Me	H	H
1-Me	7-Me	H	H	H
2-Me	7-Me	H	H	H
2-Cl	4-Cl	H	H	7-F
1-Cl	4-Cl	H	H	7-F
2-OMe	7-SMe	H	H	H
H	H	H	H	4-CF_3
2-CF_3	H	H	H	4-CF_3
4-COMe	H	H	H	H
2-OEt	H	H	H	4-Cl
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
9-OMe	H	H	H	H
2-OMe	H	H	H	H
2-OMe	4-OMe	H	H	H
1-OMe	2-OMe	4-Me	H	H
4-OMe	H	H	H	H
1-OMe	7-OMe	H	H	4-Br
1-OMe	7-OMe	2-Cl	H	4-Cl
1-OMe	7-OMe	H	H	4-Cl
	7-OMe	H	H	H
	7-OMe	H	H	4-Br

R_1	R_2	R_3	R_4	T
2-OMe	4-OH	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
		H	H	H
4-COMe	H	H	H	H
2-NHPr	4-NHPr	H	H	H
2-OME	4-CN	7-OMe	H	H
2-OMe		7-OMe	H	H
2-OMe	7-OMe	H	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-NHPr	4-NHPr	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
2-NHPr	4-NHPr	7-OMe	H	H
2-OMe	4-NH_2	7-OMe	H	H
2-OMe	4-NHPr	7-OMe	H	H
1-OMe	4-Cl	7-OMe	H	H
1-OMe	4-Br	7-OMe	H	H
1-NHPr	4-NHPr	H	H	H
1-OMe	4-CN	7-OMe	H	H
2-OMe	4-$NHCH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-S-7-Bu	7-OMe	H	H
2-OMe	4-$CH_2CO_2R^*$	7-OMe	H	H
2-OMe	4-SO_2Me	7-OMe	H	H
2-S-n-Bu	H	H	H	H
4-S-n-Bu	H	H	H	H
2-Me	4-S-n-Bu	H	H	H
2-OMe	7-Me	H	H	4-Br
2-OMe	7-CF_3	H	H	4-Br
2-OMe	7-F	H	H	4-Br
2-OMe	7-Cl	H	H	4-Br

R_1	R_2	R_3	R_4	T
2-OMe	7-Br	H	H	4-Br
2-OMe	7-NMe_2	H	H	4-Br
2-OMe	7-SMe	H	H	4-Br
2-OMe	7-SO_2Me	H	H	4-Br
2-OMe	7-Ph	H	H	4-Br
1-Me	H	H	H	4-Br
2-Me	H	H	H	H
2-OEt	H	H	H	H
7-Cl	H	H	H	H
9-Cl	H	H	H	H
7-F	H	H	H	H
7-Me	H	H	H	H
7-OMe	H	H	H	H
2-Cl	H	H	H	4-Cl
1-Me	7-Me	H	H	4-Cl
1-Me	7-Me	H	H	H
2-OMe	7-OEt	H	H	H
2-NH_2	H	H	H	H
7-OH	H	H	H	H

*pPAA = acide paraphénylacétique.

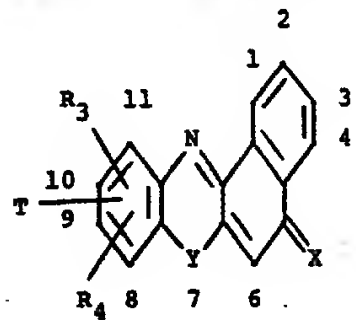
et dans laquelle R est H ou un alkyle en C_1 à C_4.

13. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sal d'un composé de formule I ou une composition pharmaceutique contenant un tel composé, dans laquelle, dans la formule I, les variables sont comme défini ci-après, X étant en position 3:

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-OMe	7-OMe	H	H	H
S	O	1-OMe	7-OMe	H	H	H
S	O	2-OMe	7-OMe	H	H	1-Br
S	O	1-OMe	7-OMe	H	H	2-Br
S	O	1-OMe	7-OMe	H	H	4-Br
S	O	1-OMe	7-OMe	H	H	2-Cl
S	O	1-OMe	7-OMe	H	H	4-Cl

Y	X	R_1	R_2	R_3	R_4	T
S	O	2-OMe	7-OMe	H	H	1-Cl
S	O	2-OMe	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OEt	H	H	1-Br
S	O	2-OEt	7-OEt	H	H	4-Br
S	O	2-OEt	7-OEt	H	H	1-Cl
S	O	2-OEt	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OMe	8-OMe	H	1-Br
S	O	2-OMe	7-OMe	8-OMe	H	4-Br
S	O	2-OMe	7-OMe	H	H	4-F
S	O	2-OMe	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OEt	H	H	4-Be
S	O	2-OMe	7-OEt	H	H	4-Cl
S	O	2-OMe	7-OEt	H	H	4-F
S	O	2-OMe	7-OEt	H	H	4-CF_3
S	O	2-OEt	7-OMe	H	H	4-Br
S	O	2-OEt	7-OMe	H	H	4-Cl
S	O	2-OEt	7-OMe	H	H	4-F
S	O	2-OEt	7-OMe	H	H	4-CF_3
S	O	2-OMe	7-OMe	H	H	4-Br

14. L'utilisation, pour la fabrication d'un médicament pour l'inhibition de la biosynthèse ou de l'action des leucotriènes chez les mammifères, d'un composé de formule I, un composé qui est un sel d'un composé de formule II:



II

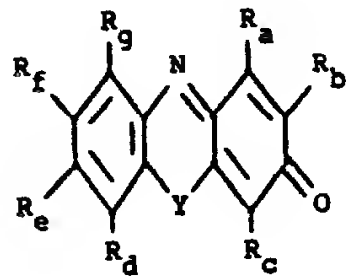
dans laquelle les substituants sont:

Y	X	R_3	R_4	T
O	O	H	H	H
S	O	H	H	H
SO	O	H	H	H

Y	X	R_3	R_4	T
SO_2	O	H	H	H
SO	O	H	H	6-Cl
S	O	6-$COCH_3$	H	H
S	O	6-CH_3	H	H
SO_2	O	6-OH	H	H
SO_2	O	6-OMe	H	H
S	O	9-OMe	H	H
S	O	6-OH	H	H
S	O	6-OMe	H	H
S	O	6-NHCOMe	H	H
S	O	6-NHPh	H	H
S	O	H	H	6-Br
S	O	6-NHMe	H	H
S	O	6-NH-t-Bu	H	H
S	O	6-NH-COMe	H	9-Cl
S	O	6-NH-COMe	9-Ome	H
S	O	6-NHPh-p-Br	H	9-Cl
O	O	H	H	6-Cl
O	O	H	H	6-Br
O	O	9-OMe	H	6-Br
O	O	9-OMe	6-NHPr	H
S	O	6-CF_3	H	H
S	O	6-S-n-Bu	H	H
S	O	6-OMe	H	9-Cl
S	O	9-OMe	H	6-Cl
S	O	6-OMe	9-OMe	H
S	O	6-Cl	9-Me	11-Br
S	O	6-NHPh	9-Me	11-Br
S	O	6-Me	H	H
O	NH	9-NMe_2	10-Me	H
O	NH	9-$N(Et)_2$	H	H
S	O	6-Cl	H	H

15. L'utilisation selon l'une quelconque des revendications 1 à 14, appliquée au traitement de (1) les affections pulmonaires, (2) l'inflammation, (3) les allergies, (4) la douleur, (5) les affections cardiovasculaires ou (6) les affections cutenées.

16. Les composés de formule:

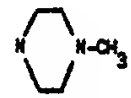
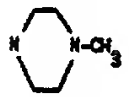
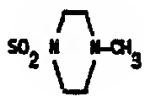
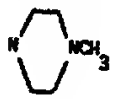


dans laquelle les substituants sont:

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	SCH_3	H	H	H	H	H
S	H	H	SCF_3	H	H	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H
S	H	H	Cl	H	CH_2OH	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
S	H	OMe	Br	H	Me	H	H
S	H	H	CHO	H	H	H	H
S	H	H	$COCF_3$	H	H	H	H
S	H	H	H	H	SCH_3	H	H
S	H	H	H	H	OCH_3	H	H
S	H	H	H	H	CO_2CH_3	H	H
S	H	H	H	H	CO_2H	H	H
S	H	H	H	H	CN	H	H
S	H	H	H	H	CHO	H	H
S	H	H	H	H	$CONH_2$	H	H
S	H	H	H	H	CH_2OH	H	H
S	H	H	H	H	CF_3	H	H
S	CH_3	H	Cl	H	H	H	H
S	H	CH_3	Cl	H	H	H	H
S	H	H	Cl	H	F	H	H
S	H	Cl	Cl	H	F	H	H
S	H	CH_3	H	H	F	H	H
S	CH_3	H	H	H	F	H	H
S	H	H	Cl	H	OMe	H	H
S	H	H	Cl	H	CF_3	H	H
S	H	H	Cl	H	CO_2Me	H	H
S	H	H	Cl	H	CO_2H	H	H
S	H	H	Cl	H	CN	H	H
S	H	H	Cl	H	CHO	H	H
S	H	H	Cl	H	$CONH_2$	H	H

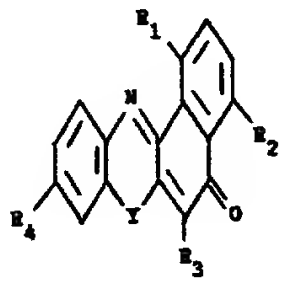
Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
S	H	H	Cl	H	CH_2OH	H	H
S	H	H	OCH_3	H	Cl	H	H
S	H	H	CF_3	H	Cl	H	H
S	H	OEt	Cl	H	H	H	H
S	H	OiPr	H	H	H	H	H
S	OMe	H	Cl	H	H	H	H
S	OEt	H	Cl	H	H	H	H
S	H	OiPr	Cl	H	H	H	H
S	H	O-benzyl	Cl	H	H	H	H
S	H	OEt	H	H	F	H	H
S	H	OCH_3	Cl	H	H	H	H
S	H	OEt	H	H	CH_3	H	H
S	H	OEt	Cl	H	F	H	H
S	H	OEt	Cl	H	CH_3	H	H
S	H	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	H	H	H
S	H	CH_3	Br	H	H	H	H
S	CH_3	H	H	H	CH_3	H	H
S	H	CH_3	H	H	CH_3	H	H
S	CH_3	H	Cl	H	CH_3	H	H
S	H	CH_3	Cl	H	CH_3	H	H
S	Cl	H	Cl	H	F	H	H
S	H	OMe	Br	H	OMe	H	H
S	H	OMe	Cl	H	OMe	H	H
S	H	OEt	Br	H	OEt	H	H
S	H	OEt	Cl	H	OEt	H	H
S	H	OMe	Cl	H	OEt	H	H
S	H	OMe	H	H	SMe	H	H
O	H	OMe	Br	H	OMe	H	H
O	H	OMe	Cl	H	OMe	H	H
O	H	H	Cl	H	H	H	H
S	H	OMe	Br	H	Me	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
SO_2	H	H	OH	H	H	H	H
SO_2	H	OMe	OH	H	OMe	H	H
SO_2	OMe	OMe	Me	H	H	H	H
SO_2	H	H	OMe	H	H	H	H
SO_2	H	OMe	OMe	H	OMe	H	H
S	H	H	H	H	H	H	OCH_3
S	H	OCH_3	H	H	F	H	H
S	H	OCH_3H	OCH_3	H	H	H	H
S	OCH_3	OCH_3	Me	H	H	H	H
S	H	H	$COCH_3$	H	H	H	H
S	OCH_3	H	Br	H	OCH_3	H	H
S	OCH_3	Cl	Cl	H	OCH_3	H	H
S	OCH_3	H	Cl	H	OCH_3H	H	H
S	H		H	H	OCH_3	H	H
S	H		Br	H	OCH_3	H	H
SO_2	H	OCH_3	OH	H	OCH_3	H	H
SO_2	NHPr	H	NHPr	H	H	H	H
SO_2		H		H	H	H	H
SO_2	H	OCH_3		H	OCH_3	H	H
SO_2	H	OCH_3	Br	H	OCH_3	H	H
S	NHPR	H	NHPr	H	H	H	H
S	NHPr	H	NHPr	H	OCH_3	H	H
S	H	NHPr	NHPr	H	H	H	H
S	H	NHPr	NHPr	H	OCH_3	H	H
S	H	OCH_3	NH_2	H	OCH_3	H	H
S	H	OCH_3	NHPr	H	OCH_3	H	H
SO_2	H	OCH_3	NHPr	H	OCH_3	H	H
O	OCH_3	H	Cl	H	OCH_3	H	H

Y	R_a	R_b	R_c	R_d	R_e	R_f	R_g
O	OCH_3	H	Br	H	OCH_3	H	H
O	NHPr	H	NHPr	H	H	H	H
SO_2	H	OCH_3	CN	H	OCH_3	H	H
SO_2	H	OCH_3	$NHCH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	S-N-Bu	H	OCH_3	H	H
SO_2	H	OCH_3	$CH_2CO_2R^*$	H	OCH_3	H	H
SO_2	H	OCH_3	SO_2CH_3	H	OCH_3	H	H
S	H	S-n-Bu	H	H	H	H	H
S	H	H	S-n-Bu	H	H	H	H
S	H	CH_3	S-n-Bu	H	H	H	H
S	H	OMe	Br	H	CF_3	H	H
S	H	OMe	Br	H	F	H	H
S	H	OMe	Br	H	Cl	H	H
S	H	OMe	Br	H	Br	H	H
S	H	OMe	Br	H	NMe_2	H	H
S	H	OMe	Br	H	SMe	H	H
S	H	OMe	Br	H	SO_2Me	H	H
S	H	OMe	Br	H	Ph	H	H
S	H	H	H	Cl	OMe	H	H

et R est H ou un alkyle en C_2 à C_4.

17. Les composés de formule:



dans laquelle les substituants sont:

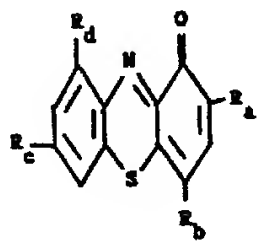
Y	R_1	R_2	R_3	R_4
S	H	H	S-n-CH_4H_9	H
S	OH	H	CH_3	H
S	OCH_3	H	CH_3	H
S	H	H	F	H

Y	R_1	R_2	R_3	R_4
S	H	H	CF_3	H
S	H	H	Cl	CF_3
S	H	H	Cl	SCH_3
S	H	H	Br	Cl
S	H	H	CH_3	Br
S	H	H	F	Br
S	H	H	$COCH_3$	Cl
S	H	H	CF_3	CH_3
S	H	H	SC_4H_9	CH_3
S	H	H	CF_3	Cl
S	H	H	Cl	CH_2COOR
S	H	H	Cl	$CH(Me)CO_2R$
S	H	H	Cl	$COCH_3$
S	H	H	H	Cl
S	H	H	H	Br
S	H	H	H	F
S	H	H	H	CF_3
S	H	H	H	CH_3
S	H	H	H	CH_2OH
S	H	H	H	OCH_3
S	H	H	H	SCH_3
S	H	H	H	COOR
S	H	H	H	CH_2CO_2R
S	H	H	H	$CH(Me)CO_2R$
SO_2	H	H	NHPr	H
SO_2	H	H		H
SO_2	H	H	NH_2	H
SO_2	H	H	NHPr	OCH_3
S	-1,4-dihydro-		H	H
S	H	H	NHPr	OCH_3
O	H	H	Cl	H

Y	R_1	R_2	R_3	R_4
O	H	H	Br	H
O	H	H	Br	OCH_3
O	H	H	NHPr	OCH_3

et dans laquelle R est H ou un alkyle en C_1 à C_4.

18. Les composés de formula:



III

dans lequelle les substituants sont:

R_a	R_b	R_c	R_d
t-Bu	t-Bu	H	H
t-Bu	t-Bu	F	H
t-Bu	t-Bu	Me	H
t-Bu	t-Bu	SMe	H
t-Bu	t-Bu	H	OMa

19. Les composés 2-S-glutathionyl-3H-phénothiazine-3-one et 4-chloro-2-S-glutathionylphénothiazine-3-ona.

20. L'utilisation, selon la revendication 1, pour la fabrication d'un médicament qui contiant de plus un second ingrédient actif qui est un agent anti-inflammatoire non stéroïdien; un agent aneigésique périphérique; un inhibiteur de la cyclooxygénase; un antagoniste des leucotriènes; un agent antihisteminiqua; un antagoniste des prostaglandines; ou un antagoniste du thromboxane, dens lequel le rapport pondéral du composé de formule I au second ingrédient actif est dans la gamme de 10/1 à 1/10.